THE PIERS (PRE-ECLAMPSIA INTEGRATED ESTIMATE OF RISK) MODEL: DEVELOPMENT OF A VALID OUTCOME PREDICTION MODEL FOR PRE-ECLAMPSIA

by

JENNIFER MARIE MENZIES

B.Sc., The University of British Columbia, 2002

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES
(Reproductive and Developmental Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

April 2009

© Jennifer Marie Menzies, 2009
ABSTRACT

Objective: This research responded to the need to define evidence-based criteria of maternal risk by developing a model - the Pre-eclampsia Integrated Estimate of RiSk (or PIERS) model – that predicts a combined adverse maternal outcome (mortality and/or significant morbidities) within 48 hour of, and up to seven days after, admission with pre-eclampsia (study eligibility).

Methods: Prospective data for this project came from the PIERS study database (1259 women, seven international tertiary centers, 4 year period). Part 1. Using PIERS data and retrospective data from BC Women’s Hospital, the impact of standardized assessment and surveillance (standing orders) on the incidence of adverse maternal outcomes was assessed. Part 2. Criteria of ‘severe’ disease were assessed against their ability to identify maternal risk. Part 3. For PIERS model development and initial validation, independent predictor variables were selected through univariable logistic regression and tests of correlation and co-linearity. The fitted models were derived using multivariate logistic regression, predictive performance evaluated using area under the receiver-operator curve [AUC], and initial validation by cross-validation.

Results: Part 1. Introducing standing orders reduced the incidence of adverse maternal outcomes (5.1% to 0.7%; OR 0.14 [0.04, 0.49]). Part 2. Most Canadian and American severity criteria did not predict adverse outcomes. Part 3. Two PIERS outcome prediction models were developed and initially validated. The fullPIERS model (AUC 0.906 [0.851, 0.961]), for use in well-resourced settings, comprises six independent clinical and laboratory variables. The miniPIERS model (AUC 0.817 [0.738, 0.896]), for
use in minimally-resourced settings, comprises three independent clinical variables. Both models (fitted and cross-validated) maintain AUC>0.7 up to seven days after eligibility.

**Conclusion:** Standardized assessment and surveillance of women with pre-eclampsia reduces maternal risks. Published criteria of ‘severe’ disease do not denote increased maternal risk. The two pre-eclampsia-specific outcome prediction models, fullPIERS and miniPIERS, identify maternal risk up to 7 days before complications arise.
# TABLE OF CONTENTS

Abstract ............................................................................................................................... ii

Table of Contents ............................................................................................................... iv

List of Tables ................................................................................................................... viii

List of Figures .................................................................................................................... ix

Acknowledgements .............................................................................................................. x

Co-Authorship Statement................................................................................................... xi

CHAPTER 1  Introduction ................................................................................................. 1

1.1 Background .................................................................................................................. 1
    1.1.1 Pre-eclampsia and its importance ................................................................. 1
    1.1.2 The variable clinical presentation of pre-eclampsia .................................... 2
    1.1.3 The pathogenesis of pre-eclampsia .............................................................. 3
    1.1.4 Current classification and evaluation of pre-eclampsia .............................. 4
    1.1.5 Management of pre-eclampsia pregnancies .............................................. 6
    1.1.6 Predictors of adverse outcomes associated with pre-eclampsia............ 7

1.2 Existing Predictive Models ....................................................................................... 8
    1.2.1 Acute Physiology and Chronic Health Evaluation (APACHE) score ........... 8
    1.2.2 Multiple Organ Dysfunction Syndrome (MODS) score .......................... 10
    1.2.3 Brussels score ............................................................................................ 12
    1.2.4 The need for a predictive model for pre-eclampsia ................................. 13

1.3 The Development of a Predictive Model Specific to Pre-eclampsia ................. 14
    1.3.1 Objectives for predictive models ............................................................... 14
    1.3.2 Methodological standards ......................................................................... 15
    1.3.3 Item selection ............................................................................................ 15

1.4 Research Questions and Objectives ..................................................................... 15

1.5 Tables and Figures ................................................................................................. 18

1.6 References ............................................................................................................. 20
CHAPTER 2  Instituting Surveillance Guidelines and Adverse Outcomes in Pre-eclampsia .................................................................25

2.1 Materials and Methods ...................................................................................................................26

2.2 Results ........................................................................................................................................29

2.3 Discussion ....................................................................................................................................30

2.4 Tables and Figures ......................................................................................................................36

2.5 References ..................................................................................................................................39

CHAPTER 3  Current CHS and NHBPEP Criteria for Severe Pre-eclampsia Do Not Uniformly Predict Adverse Maternal or Perinatal Outcomes ..........42

3.1 Methods .........................................................................................................................................43

3.1.1 Factors measured at presentation to ‘predict’ the severity of pre-eclampsia ..............45

3.1.2 Factors used to define adverse maternal and perinatal outcomes ..........................46

3.1.3 Statistical analyses ............................................................................................................47

3.2 Results .........................................................................................................................................47

3.3 Discussion .....................................................................................................................................49

3.4 Conclusion ....................................................................................................................................51

3.5 Tables and Figures ......................................................................................................................53

3.6 References ..................................................................................................................................58

CHAPTER 4  Predicting Adverse Maternal Outcomes in Pre-eclampsia: The PIERS (Pre-eclampsia Integrated Estimate of RiSk) Models-
Development and Initial Validation .................................................................................................60

4.1 Methods .........................................................................................................................................62

4.1.1 Data sources ..........................................................................................................................65

4.1.2 Bias and missing data ...........................................................................................................66

4.1.3 Study size ..............................................................................................................................67

4.1.4 Quantitative variables ...........................................................................................................68

4.1.5 Statistical methods ...............................................................................................................68

4.2 Results .........................................................................................................................................70
4.3 Discussion ...................................................................................................................73
   4.3.1 Key results ............................................................................................................73
   4.3.2 Limitations ..........................................................................................................74
   4.3.3 Interpretation .......................................................................................................75
   4.3.4 Generalisability ...............................................................................................78

4.4 Tables and Figures .....................................................................................................81

4.5 References .................................................................................................................96

CHAPTER 5 Discussions and Conclusions ....................................................................100
   5.1 Principal Findings ....................................................................................................100
      5.1.1 Severity criteria are not associated with adverse outcomes .......................100
      5.1.2 The developed PIERS models can predict maternal risk .........................101
      5.1.3 Component variables included in the PIERS models ................................103
      5.1.4 Component variables excluded in the PIERS models ...............................104

   5.2 Strengths and Limitations .....................................................................................106
      5.2.1 Strengths attributed to the PIERS study .....................................................106
      5.2.2 Limitations attributed to the PIERS study ..................................................107

   5.3 Comparisons to Relevant Studies ..........................................................................110
      5.3.1 Utilizing the APACHE II illness severity score in the setting of eclampsia ...110
      5.3.2 Previous studies attempting to develop outcome prediction models specific to pre-eclampsia .................................................................111

   5.4 Implications and Applications for Clinicians and Researchers .............................114

   5.5 Conclusion ..............................................................................................................115

   5.6 Future Directions ..................................................................................................116
      5.6.1 Re-validation of the PIERS models ............................................................116
      5.6.2 Development of the PIERS scoring system ..............................................116
      5.6.3 Implementation of the PIERS models into routine clinical use ...............117
      5.6.4 Economic analyses ....................................................................................118
      5.6.5 Development of a perinatal outcome prediction model .........................119

   5.7 References .............................................................................................................120
APPENDIX A  Detailed Methodologies .................................................................123
    A1  Study Design ...............................................................................................123
        A1.1 Sites .......................................................................................................123
        A1.2 Inclusion/Exclusion criteria .................................................................124
        A1.3 Standing orders ......................................................................................126
        A1.4 Selection of candidate predictor variables .........................................127
        A1.5 Combined adverse maternal outcome ...............................................129
        A1.6 Combined adverse perinatal outcome ...............................................135
    A2  Data ............................................................................................................136
        A2.1 PIERS case report form development ..................................................136
        A2.2 PIERS database development ...............................................................140
        A2.3 Data collection .......................................................................................140
    A3  Statistical plan and methods ......................................................................141
        A3.1 Sample size ............................................................................................141
        A3.2 Data sources ..........................................................................................143
        A3.3 Statistical methods ...............................................................................143
    A4  References .................................................................................................146

APPENDIX B  PIERS Case Report Forms ...............................................................149

APPENDIX C  UBC Clinical Research Ethics Board Certificates of Approval ...........175
LIST OF TABLES

Table 1.1 Classification of the hypertensive disorders of pregnancy .......................19
Table 2.1 Baseline characteristics ............................................................................36
Table 2.2 Adverse maternal outcome .....................................................................37
Table 2.3 Adverse perinatal outcome .....................................................................38
Table 3.1 Canadian Hypertension Society (CHS) and National High Blood Pressure Education Program (NHBPEP) candidate predictors of severe pre-eclampsia.................................................................53
Table 3.2 Baseline characteristics of 737 women at entry into PIERS.......................54
Table 3.3 Adverse maternal and perinatal outcomes ..............................................55
Table 3.4a Canadian Hypertension Society (CHS) severity criteria and their relationship with adverse maternal and perinatal outcome ........................................56
Table 3.4b National High Blood Pressure Education Program (NHBPEP) severity criteria and their relationship with adverse maternal and perinatal outcome .................................................................57
Table 4.1 Variables considered in the PIERS modeling ........................................81
Table 4.2 Characteristics of women in the PIERS study .......................................83
Table 4.3 Adverse outcomes ................................................................................85
Table 4.4 Univariable analyses of candidate predictor variables with p<0.1 and collected in >80% of cases........................................................................86
Table 4.5 Univariable analyses of all candidate predictor variables investigated .....93
**LIST OF FIGURES**

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1.1</td>
<td>The pathogenesis of pre-eclampsia</td>
<td>18</td>
</tr>
<tr>
<td>Figure 4.1a</td>
<td>Cluster analyses of continuous variables significantly associated with the combined adverse maternal outcome by univariable analysis</td>
<td>88</td>
</tr>
<tr>
<td>Figure 4.1b</td>
<td>Cluster analysis of dichotomous variables significantly associated with the combined adverse maternal outcome by univariable analysis</td>
<td>89</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Performance of the fullPIERS model developed with data from first 48h after eligibility and first 24h after eligibility</td>
<td>90</td>
</tr>
<tr>
<td>Figure 4.3</td>
<td>Performance of the miniPIERS model developed with data from first 48h after eligibility and first 24h after eligibility</td>
<td>91</td>
</tr>
<tr>
<td>Figure 4.4</td>
<td>fullPIERS and miniPIERS areas under the receiver-operator curves from 2-7 days after PIERS study eligibility including the fitted models and cross validation</td>
<td>92</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

I would like to offer sincere thanks to my supervisors who have provided me with the guidance, support and encouragement to achieve my goals, both academically and professionally. You have generously taken the time to share your knowledge, and have inspired me with your unwavering dedication to your work. I will be forever grateful for the opportunities that you have given me.

I would also like to thank the Canadian Institutes of Health Research (CIHR) who have provided financial support for my training through the Strategic Training Initiative in Research in Reproductive Health Sciences (STIRRHS) program.

Thank you also to all of the co-investigators, research co-coordinators and research assistants involved in the international PIERS project, who have been integral to the success of the PIERS program of research.

Thank you to my colleagues and friends, both past and present, in the Maternal Fetal Medicine Research corridor at BC Women’s Hospital and Health Centre, especially to Jing (Larry) Li, Brandon Baraty, Jonathan Lam and Beth Payne. Special thanks also to statisticians Ying MacNab, Yi Lin and Xiang (Sam) Xuan for their assistance with the data analyses.

Lastly, but most importantly, thank you to my family for your unconditional love, patience and support. I could not have accomplished this goal without your encouragement and I share this achievement with you.
CO-AUTHORSHIP STATEMENT

Overall, the co-authors to the three included manuscripts (Chapters 2-4) have contributed to the identification and design of the research program, and to the preparation and revision of the manuscripts. Acknowledgement must also be made to the local coordinator(s) and research assistants at each of the 7 collaborating international sites, who were responsible for the data collection performed at each of these sites.

Overall, the thesis author is responsible for the direction and coordination of the research program as a whole, the creation of the study case report forms and working protocols used for all prospective data collection, the performance of a portion of the data collection at the Vancouver site, the monitoring of all submitted data for completeness and accuracy, and a portion of the preparation and revision of the three manuscripts.

As contributions to the performance of the data analyses differed between the manuscripts, the details are provided separately below:

**First included manuscript (Chapter 2):** The thesis author is responsible for all of the data analyses performed, with guidance provided by co-authors PvD and YMacN.

**Second included manuscript (Chapter 3):** The thesis author is responsible for all of the data analyses performed, with guidance provided by co-authors LAM and YMacN.

**Third included manuscript (Chapter 4):** Co-authors and statisticians YMacN and YL were responsible for the performance of all data analyses performed and presented in the manuscript, and for the preparation of the statistical methods portion of this manuscript.
CHAPTER 1

Introduction

1.1 Background

1.1.1 Pre-eclampsia and its importance

Pre-eclampsia is a disorder that occurs specifically during pregnancy and the immediate postpartum period. Pre-eclampsia complicates at least 3-5% of pregnancies and remains one of the two most common causes of maternal death in the Developed and Developing World (1-3). Along with thromboembolic disease, pre-eclampsia is the most common cause of direct maternal mortality in Canada (2). The World Health Organization estimates that pre-eclampsia results in over 76,000 maternal deaths per annum (1); this equates to the death of one woman at least every seven minutes worldwide.

Pre-eclampsia typically occurs in middle to late pregnancy (after 20 weeks’ gestation), although onset is unpredictable and it can occur earlier. It is particularly dangerous, for both mother and baby, when onset occurs early in pregnancy. Early onset pre-eclampsia (i.e. onset of at <32 weeks’ gestation) is associated with a dramatic increase in the risk of maternal death compared with pre-eclampsia occurring at term (36-40 weeks’ gestation) (4). Pre-eclampsia is curable only by termination of the pregnancy, and so the definitive treatment for this condition is delivery. While this is the treatment of choice for the mother, it is not always the best option for the fetus, especially if remote from term (<32-34 weeks) (5;6). Such a premature fetus is at high risk for perinatal
morbidity and mortality. Although those fetuses delivered closer to term are at lower risk, complications attributable to iatrogenic prematurity are still important to consider as most pre-eclampsia emerges near term (7).

As a consequence of the high maternal and perinatal morbidity and mortality associated with it, pre-eclampsia also carries significant cost implications. In the USA, it is estimated that pre-eclampsia costs more than $7.5 billion each year, of which $3 billion is spent on maternal illness, and $4.5 billion on infant illness (8).

### 1.1.2 The variable clinical presentation of pre-eclampsia

Pre-eclampsia has both maternal and fetal syndromes. Each syndrome in turn is characterized by several clinical manifestations. The maternal syndrome of pre-eclampsia is usually defined by its most common and most easily recognizable maternal manifestations of hypertension (BP ≥ 140/90mmHg) and proteinuria (> 0.3g/24h) that appear after 20 weeks’ gestation and regress after pregnancy. However, the maternal syndrome of pre-eclampsia is far more complex than just hypertension alone (9). It is also a form of systemic inflammation, sharing many similarities with the systemic inflammatory response syndrome (SIRS) (10). A noted consequence of this systemic inflammation is multiple organ dysfunction, which also characterizes the maternal syndrome of pre-eclampsia (10). In fact, in an era of good BP control (11;12), maternal mortality associated with pre-eclampsia is most commonly due to either hepatic necrosis or the acute respiratory distress syndrome, both of which are consequences of systemic inflammation (10).
The fetal syndrome of pre-eclampsia is manifested by intrauterine growth restriction (IUGR), oligohydramnios, abnormal umbilical artery Doppler velocimetry and/or fetal acidaemia. Pre-eclampsia also poses an increased risk of both perinatal morbidity and mortality, especially due to the risks of iatrogenic prematurity.

1.1.3 The pathogenesis of pre-eclampsia

Although the exact etiology of pre-eclampsia is not currently known, there is evidence to suggest that it may have its origins in early pregnancy with abnormal placentation, by which an inadequate vascular response to the placentation process subsequently results in reduced placental perfusion (13). The consequences of this poor placentation become evident later in pregnancy as fetal demands surpass available placental supply, creating a ‘uteroplacental mismatch’ (14). This ‘mismatch’ may also occur in the circumstance of normal placentation when there are excessive fetal demands, as can occur in a multiple pregnancy (15), or cases of fetal overgrowth (16). When this discrepancy between pregnancy demands and placental supply occurs, the intervillous space of the mismatched placenta releases factors, or an ‘intervillous soup’ (14), into the maternal circulation. These blood-borne factors are believed to lead to endothelial dysfunction (17), microangiopathic haemolysis (17), and inflammation (18-21), which in turn affect virtually all maternal organ systems leading to the multiple organ dysfunction typical of the clinical maternal syndrome of pre-eclampsia (Figure 1.1).
1.1.4 Current classification and evaluation of pre-eclampsia

At the time of this study, guidelines for the diagnosis, classification and management of pre-eclampsia had been produced by the Canadian Hypertension Society (CHS) in 1997 (22), the US National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (NHBPEP) in 2000 (23), and the Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) in 2000 (24). These publications classify pre-eclampsia as being either mild or severe (Table 1.1).

Mild pre-eclampsia is most commonly defined as a blood pressure (BP) ≥ 140/90 mmHg with proteinuria of ≥0.3-3g/24h. Severe pre-eclampsia is classified as mild pre-eclampsia with a single additional ‘adverse feature’ such as very high blood pressure (i.e. BP ≥ 160-170/100-110 mmHg), heavy proteinuria of ≥3-5g/24h, and/or the occurrence of symptoms such as headache or visual disturbances (22-24).

These guidelines also recommend routine evaluations of maternal and fetal well-being for pregnancies complicated with pre-eclampsia. Maternal well-being is assessed by maternal blood and urine tests to evaluate vulnerable end organ function (or dysfunction) in several organ systems. Fetal well-being is evaluated by ultrasounds and fetal heart rate analysis. Despite having published guidelines in place, it has been documented that the surveillance of women with suspected or confirmed pre-eclampsia is still quite variable between Canadian practitioners (25).

In addition, all of these guidelines have limitations. Firstly, all are based largely on expert opinion rather than on high quality evidence. The 1997 CHS report states that much of the recommendations for evaluation given are grade C or D, meaning that they are based on borderline evidence or include expert opinion (22). The 1997 CHS
classification is also based mainly on retrospective diagnosis and not on the clinical picture at presentation when plans for management are made. For example, 35% of women who present with gestational hypertension at <34 weeks’ gestation will develop proteinuria up to eight weeks later, and meet the diagnostic criteria for pre-eclampsia (7). Thus, even in cases of either non-proteinuric gestational hypertension or non-hypertensive gestational proteinuria, pre-eclampsia should be considered, investigated and ruled out.

Secondly, most classifications require the occurrence of both hypertension and proteinuria. However this clinical picture fails to develop within a week prior to the occurrence of an eclamptic seizure in 40% of women (26). Other maternal and fetal features may also be important in the classification of pre-eclampsia.

Thirdly, these systems dichotomize pre-eclampsia into either mild or severe disease, not allowing for any stratification of the clinical presentations of pre-eclampsia that may occur in between.

And finally, none of these classification systems take into account gestational age, which is the most important indicator of both maternal and perinatal outcomes. Early onset pre-eclampsia (<32 weeks’ gestation) is associated with a risk of maternal mortality that is 20-fold higher compared with onset which occurs at term (36-40 weeks’ gestation or more) (4). A greater than 50% chance of intact fetal survival in pre-eclampsia transpires only when gestational age at delivery is ≥27 weeks’ or the birthweight ≥ 600g (6). However, each additional week of gestation gained results in substantial benefit in perinatal outcome (5;6), as gestational age among euploid fetuses is the most important determinant of perinatal outcome (11;27;28).
The 1997 CHS guidelines have since been updated under the auspices of the Society of Obstetricians and Gynaecologists of Canada (SOGC) in 2008 (29); however, even in this updated document, the issues surrounding dichotomous classifications based on severity criteria still exists.

1.1.5 Management of pre-eclampsia pregnancies

Currently, management of pre-eclampsia is guided primarily by clinical impression rather than by evidence-based criteria of disease severity. It is widely known that the definitive treatment for pre-eclampsia is always delivery for the mother, but this is not always the best option for the fetus. Evidence from randomized controlled trials (RCTs) has shown that, remote from term, pregnancy prolongation by expectant therapy (delaying delivery until compelled by either maternal or fetal condition) decreases serious perinatal morbidity without increasing maternal risk (11;27;28). However, these RCTs did not have adequate power to distinguish a difference in the occurrence of serious maternal outcomes between groups, and this uncertainty regarding the degree of maternal risk (30) associated with expectant management has made some clinicians hesitant to practice it. In Canada, the CHS has not made any recommendations for when to deliver women with pre-eclampsia, but expectant management closer to term (≥ 34 weeks’ gestation) has been endorsed by Canadian practitioners (25;31), in order to allow for fetal maturation to achieve better perinatal outcomes. To facilitate improvements in the clinical management and care of women with pre-eclampsia, it is important to be able to identify those women who are at increased risk of developing serious adverse outcome,
and, by this process of exclusion, identify those women for whom expectant management is a viable option (11).

1.1.6 Predictors of adverse outcomes associated with pre-eclampsia

At present, it is extremely difficult to identify which mothers with pre-eclampsia are at increased risk of developing adverse maternal complications, and this risk cannot be graded. Hypertension and proteinuria are commonly recognized risk factors for adverse maternal or perinatal outcome in pre-eclampsia pregnancies, and, as such, are often used to differentiate between mild and severe disease (22-24). Both heavy proteinuria and severe maternal hypertension are listed as ‘adverse features’ of pre-eclampsia in the CHS guidelines (22). However, this dichotomous classification of pre-eclampsia into mild or severe disease has not been shown to be related to quantifiable maternal risk. It was also not known which of the proposed ‘adverse features’ listed by the CHS are truly predictive of adverse maternal and/or perinatal outcomes, or to what degree. There may also be other factors, such as gestational age, which are not included in the guidelines but that may also be predictive of adverse maternal outcome; clearly gestational age identifies perinatal risks. Thus, once again it is clear that in order to improve maternal and perinatal outcomes in pre-eclampsia pregnancies, we need to be able to compare quantifiable maternal risk with quantifiable perinatal risks, and identify which pregnancies can be safely prolonged.
1.2 Existing predictive models

Illness severity models, such as the Acute Physiology and Chronic Health Evaluation (APACHE) (32;33), Multiple Organ Dysfunction (MOD) (34), and Brussels (35) scoring systems, have been previously developed to quantify severity of disease in patients admitted to intensive care unit (ICU) settings, allowing for the stratification of patients according to risk of hospital mortality. As many patients admitted to ICUs fulfill the criteria for the systemic inflammatory response syndrome (SIRS), an inflammatory state of the entire body without a proven source of infection, which pre-eclampsia has been noted to resemble to a significant degree (10), we considered the utility of such illness severity scoring systems in the context of pre-eclampsia.

1.2.1 Acute Physiology and Chronic Health Evaluation (APACHE) Score

The APACHE score is a classification system designed to measure the severity of disease for critically ill adult patients admitted to intensive care units (ICU) in order to objectively predict risk for hospital mortality (36-38). This knowledge of risk is then able to inform decisions surrounding resource utilization, initiation or continuation of therapy, and timing of discharge (39-41).

Since its inception in 1981, the APACHE scoring system has evolved through 3 iterations, and is based on the premise that acute abnormalities in the physiologic balance of a patient are quantifiably associated with short-term risk of death (36-38). The most current APACHE score, APACHE III, ranges from a total score of 0 to 299 and is calculated by summing points for three groups of variables: age (0 to 24 points), 17
individual physiologic measurements (0 to 48 points for an individual variable, for a total range from 0 to 252), and a chronic health evaluation of 7 potential comorbid conditions (0 to 23 points) (38).

Component weights for the 17 physiologic variables, were estimated using multivariable logistic regression analyses using half of the compiled database, and were validated in the remaining independent half (38). In APACHE III, as in the previous APACHE II, weighting for each variable was determined by derangement from a normal range using specific physiologic cut points, however APACHE III assigns additional weight to extreme measurements and incorporates narrower ranges for normal or zero weight than were used in APACHE II (37;38). The recorded value utilized in assigning points for each variable is still the worst value measured over the initial 24 hours of ICU care (with missing physiologic data being assigned a zero, or “normal” weight), and an increasing APACHE III score is still closely correlated with predicted risk of hospital death (38).

When calculating the APACHE III score from data obtained during the first day of ICU stay, the discrimination and explanatory power of this first-day APACHE III equation were excellent, with an area under receiver operating curve of 0.90, and a risk estimate for hospital death that was within 3 percent of that actually observed for 95 percent of ICU admissions (38). The APACHE system thus maintains its standing as an accurate and reliable means of classifying ICU patients according to risk of hospital mortality.

However, mortality due to pre-eclampsia in the Developed World is a relatively uncommon event (4) and thus it is difficult to generalise APACHE for use in patients
with pre-eclampsia (42). Also many physiological variables are altered during pregnancy, and this gestational variation in laboratory values is not accounted for in APACHE (42;43). Taking these points into consideration, it is perhaps not surprising that the APACHE II score did not perform well in predicting mortality among eclamptic women in the intensive care unit setting, with the Glasgow coma score outperforming APACHE II in predicting maternal mortality (42).

1.2.2 Multiple Organ Dysfunction (MOD) Score

The multiple organ dysfunction syndrome (MODS) is recognized as a leading cause of both morbidity and mortality in patients admitted to intensive care units (ICUs) (44-46), and is characterised by the development of physiologic dysfunction in two or more organ systems after a disruption to systemic homeostasis (47), stemming from such acute events as infection, non-infectious inflammatory conditions, toxin exposure and immune system activation, among others (44-46).

The MOD Score was developed as a physiology-based scale to quantify the severity of the multiple organ dysfunction syndrome as an outcome measure (rather than as a predictive index) in ICU settings, in response to the notable heterogeneity of the criteria used to define the clinical syndrome (34). The MOD Score was constructed using simple physiologic measures of dysfunction in six organ systems (respiratory, renal, hepatic, cardiovascular, hematologic and neurologic) and was found to correlate strongly with the ultimate risk of ICU mortality (34). The organ systems included and the variables commonly used to assess dysfunction within each system were identified by a literature review of previously published clinical studies of multiple organ failure to
maximize construct validity (34). These candidate variables indicating organ dysfunction were further evaluated for their content and criterion validity and the best descriptive variable for each organ system was eventually chosen for inclusion in the aggregate MOD Score (34).

Through the development and validation of the MOD Score, intervals for the most abnormal value of each variable in each organ system were established and confirmed, with the intent that each organ system would contribute equally to the final score. These intervals were graded on a five-point scale (scores ranging from 0 to 4) based on correlations with ICU mortality rates, with a score of 0 reflecting essentially normal function and correlating with an ICU mortality rate of <5%, while a score of 4 reflected significant organ dysfunction and correlated with an ICU mortality rate of ≥50% (34). The ultimate MOD Score is calculated by summing maximal scores for each variable in each of the six included organ systems over the ICU stay, and, when calculated for each patient in both the development and validation sets of cases, increasing MOD Score values were found to correlate strongly with ICU mortality rate both when measured on the first day of ICU admission as a predictive indicator and when calculated over the ICU stay as an outcome measure (34). Performance of the MOD Score in both the development and validation sets, was evaluated using the area under a receiver operating curve (as explained further in Appendix A), and the results indicated that the score showed excellent discrimination in both datasets, with areas under the curve of 0.936 and 0.928 respectively (34).

However, like the APACHE score, the MOD Score was developed and validated in an ICU setting based on correlations with ultimate risk of mortality, and does not take
into account the gestational variation in laboratory values of the tests used to evaluate organ dysfunction.

1.2.3 The Brussels Score

The Brussels score was developed through a succession of consensus conferences taking place in 1993 & 1994 (35). The score predicts ICU mortality by assessing organ dysfunction in six organ systems using one organ-specific physiologic variable for each: coagulation (platelet count), hepatic (bilirubin), cardiovascular (systolic blood pressure), central nervous system (Glasgow Coma Score), renal (creatinine) and pulmonary (PaO₂/FIO₂ ratio) (35). Each system is scored on the basis of five gradations of severity: normal function, mild dysfunction, moderate dysfunction, severe dysfunction and extreme dysfunction (35). The latter three gradations represent clinically significant organ dysfunction and are differentiated from normal function and mild dysfunction by a dichotomous cut-point specific to each system (35).

For each variable, the most abnormal value measured in a given day in the ICU is utilized for calculating the Brussels score on that particular day, and missing data are carried forward from the most recent previous data available (35). In addition to predicting mortality, the Brussels score can also be used to describe morbidity. For example, use of the Brussels score to calculate Organ Failure Free (OFF) days (the number of days that a patient is both alive and free of clinically significant organ dysfunction), has been found to be a sensitive outcome measure in clinical trials, both when calculated for individual organ systems, or as a composite of two or more systems (48;49).
Again, as has been noted with the APACHE and MOD scores, the Brussels score was developed to predict mortality in an ICU setting, and does not account for the gestational variation in the physiologic variables used to evaluate function (or dysfunction) in each of the included organ systems.

1.2.4 The need for a predictive model specific to pre-eclampsia

These scores have performed well when modified for defined populations (50), however most of these modifications were generated for predominantly geriatric populations (51). Another shortfall of the modification of these models for pre-eclampsia is that they predict maternal mortality, which is actually a relatively rare event in the Developed World, even in women with pre-eclampsia (4), and they do not take into consideration the normal physiological adaptations to pregnancy.

Neonatal (Score for Neonatal Acute Physiology (SNAP-II)) (52) and paediatric (Paediatric RISk Mortality (PRISM) score) (53;54) illness severity models have also been developed to predict risk of in-hospital mortality in the settings of neonatal and paediatric intensive care units, respectively. While it is obvious that such scores cannot be utilized to assess maternal risk in the setting of pre-eclampsia, we can learn from the methodologies used in their development.

For the purposes of pre-eclampsia, it would be more relevant clinically to be able to predict serious maternal morbidity that would preclude safe pregnancy prolongation. A new scoring system needs to be developed which modifies the approaches taken in the development of the adult (APACHE (32;33;38), MOD (34)), paediatric (PRISM (53;54))
and neonatal (SNAP-II (52)) severity scores in existence, in order to account for the varied presentation of pre-eclampsia and the normal changes in clinical and laboratory parameters that take place in the setting of pregnancy. The development of a severity score for use in the setting of pre-eclampsia is what the research subsequently described in this text has sought to achieve.

1.3 The development of a predictive model specific to pre-eclampsia

1.3.1 Objectives for predictive models

Our planned research for the development of a model to predict maternal risk of adverse outcome in the setting of pre-eclampsia fulfills the established Altman and Lyman criteria (55) for the objectives of predictive models. These criteria are as follows:

1) Guide clinical decision making

2) Improve understanding of the disease process

3) Improve the design and analysis of clinical trials

4) Assist outcome comparison between treatment groups in non-randomised studies (in order to adjust for case mix)

5) Define at-risk groups based on prognosis

6) Predict disease outcome more accurately or parsimoniously
1.3.2 Methodological standards

There also exist several established methodological standards for the development of predictive models, which we have utilized in the development of our proposed model. These standards include: (i) selection of potential predictors, (ii) the establishment of clear definitions for the selected predictors and for the outcome(s) of interest which is to be predicted, (iii) data collection and (iv) statistical analyses taking into account potential biases (56-58).

1.3.3 Item selection

The candidate predictor variables assessed have been selected on the basis of five criteria, as described by Richardson et al (59). The items selected were:

1) Predictive (must correlate with the outcome of interest)

2) Available

3) Measurable

4) Frequent

5) Reliable

1.4 Research questions and objectives

This research was designed to test the hypothesis that a model based on a combination of prospectively collected maternal (clinical and laboratory) and fetal (ultrasound and cardiotocography) predictors can be developed to stratify women
admitted to hospital with pre-eclampsia according to incremental risk of adverse maternal outcomes.

The ultimate goal of this research was to develop and initially validate two prediction models – the Pre-eclampsia Integrated Estimate of RiSk (PIERS) models – that reflect the systemic nature of pre-eclampsia and that can be used to predict adverse maternal outcomes in pre-eclampsia pregnancies in a clinically useful manner: the fullPIERS model to incorporate clinical and laboratory variables for use in well-resourced settings, and the simplified miniPIERS model to be sign- and symptom-based for use in minimally-resourced settings. We aimed to design the most parsimonious models possible, by identifying those tests that best predict outcomes and abandoning investigations that are not informative for patient care.

These PIERS models will influence clinical management by enabling better stratification of women in terms of risk of developing adverse maternal and/or perinatal outcomes, and better identification of those women for whom expectant management is a safe practice. Facilitating the identification of women who are appropriate for pregnancy prolongation will minimize both iatrogenic prematurity, thus improving child health, as well as the maternal risks associated with pre-eclampsia.

The primary objective is to identify the specific maternal and fetal variables that are predictive of a combined adverse maternal outcome occurring within 48h of, and up to 7 days after, a diagnosis of pre-eclampsia (eligibility) for women admitted to hospital. The 48 hour epoch was chosen, because this is the time frame during which steroids are administered for the purpose of fetal lung maturation, and when decisions are made to stabilize and deliver, expectantly manage, or to arrange transfer to higher levels of
obstetric care. Having the ability to stratify maternal risk in real-time would potentially allow for improvements in both maternal and perinatal outcomes, by identifying those women for whom it is safe to practice expectant care or to transfer to higher levels of care, and those for whom it is reasonable to initiate induction of labour.

This hypothesis was tested by:

- Measuring relevant maternal (clinical and laboratory) and fetal (ultrasound and cardiotocography) parameters in patients admitted to hospital with pre-eclampsia, using prospective data collection
- Assessing these parameters through statistical analyses (univariable logistic regression, Pearson correlation and Chi-square tests, cluster analyses) to determine which are independently predictive of the occurrence of adverse maternal outcomes in these patients
- Using those predictors identified to build predictive models (the PIERS models) via multivariate logistic regression, that performs with adequate discrimination (i.e. an area under the receiver-operator curve of >0.7)
- Performing cross-validation to examine the performance of the final logistic regression models developed
1.5 Tables and Figures

Figure 1.1 The pathogenesis of pre-eclampsia

In this model of pre-eclampsia, the maternal syndrome develops from a number of alternative pathways leading to uteroplacental mismatch, whereby the fetoplacental demands outstrip the maternal circulatory supply. In response to the mismatch, and probably due in part to recurrent ischemia-reperfusion injury within the intervillous (maternal blood) space of the placenta and accelerated placental apoptosis, a soup of endothelium-damaging substrates is released with resulting endothelial cell activation and consequent development of the maternal syndrome of pre-eclampsia. Some elements of the soup, namely activated peripheral blood leukocytes, can cause direct end-organ damage. There is cross-talk between elements of the soup (not illustrated). ARDS: acute respiratory distress syndrome; ATN: acute tubular necrosis; DIC: disseminated intravascular coagulation; PBLs: peripheral blood leukocytes; PGs: eicosanoids; ROS: reactive oxygen species. (From von Dadelszen et al, Crit Care Med 2002; 30:1883-1892) (6).
<table>
<thead>
<tr>
<th>Classification of the hypertensive disorders of pregnancy*</th>
<th>CHS (1997) (22)</th>
<th>NHBPEP (23)</th>
<th>ASSHP (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing hypertension, essential/ secondary</td>
<td>Chronic hypertension</td>
<td>Chronic hypertension, essential/secondary</td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension without proteinuria, ± adverse features†</td>
<td>Transient hypertension</td>
<td>Pregnancy-induced hypertension</td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension with proteinuria, ± adverse features‡</td>
<td>Pre-eclampsia/eclampsia</td>
<td>Pre-eclampsia, mild/severe</td>
<td></td>
</tr>
<tr>
<td>Pre-existing hypertension + superimposed gestational hypertension, with proteinuria</td>
<td>Pre-eclampsia superimposed on chronic hypertension</td>
<td>Pre-eclampsia superimposed on chronic hypertension</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable antenatally</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


†Adverse features (22): convulsions; diastolic blood pressures (dBP) >110mmHg; thrombocytopenia (<100 x 10^12/L); oliguria (<500ml/d); pulmonary oedema; elevated liver enzymes; severe nausea and vomiting; frontal headache; visual disturbances; persistent right upper quadrant pain; chest pain; dyspnoea; suspected abruption; haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; intrauterine growth restriction (IUGR); oligohydramnios; absent or reversed umbilical arterial end diastolic flow (Doppler).

‡Adverse features (22): same as above plus proteinuria >3g/d and hypoalbuminaemia (<18g/L).

(From von Dadelszen et al, *J Obstet Gynaecol Can* 2004; 26:871-879 (60). This table extracted from this article is provided free of charge courtesy of The Society of Obstetricians and Gynaecologists of Canada (SOGC).)


1.6 References


Pre-eclampsia remains a leading cause of maternal mortality in North America, and we have found that the surveillance of women with suspected or confirmed pre-eclampsia is variable between practitioners (1). The mainstays of the management of severe pre-eclampsia include “full assessment of the mother and the baby, and delivery on the best day in the best way (2).”

It has been observed that standardizing care is associated with reduced adverse health outcomes across a range of disciplines and medical conditions (3-14). Failure to standardize care has been associated with poorer outcomes (14).

We have previously undertaken a multicentre retrospective study of two years' pre-eclampsia cases in three tertiary level units (15). In that study, we tested a number of predictors of adverse maternal outcomes against a combined adverse maternal outcome derived by international Delphic consensus(16;17). This combined adverse outcome reflects the systemic inflammatory nature of the maternal syndrome (18;19) and assesses all vulnerable organ systems (18). In an era of generally adequate blood pressure control, maternal mortality associated with pre-eclampsia is largely due to the complications of systemic inflammation (19).
Since the time of the retrospective study, we have developed guidelines for the assessment and ongoing evaluation of women admitted to our unit with a suspected or confirmed hypertensive disorder of pregnancy. Part of a continuous quality improvement (CQI) initiative at BC Women’s Hospital and Health Centre (BC Women’s), these guidelines were designed to evaluate comprehensively vulnerable organ function, and to reflect both the variable presentation and the systemic nature of pre-eclampsia (gestational hypertension with either proteinuria or adverse conditions) and the other hypertensive disorders of pregnancy. They were derived from the pattern of investigation used in other centers of excellence, and in response to international guidelines (20-22), to current practice across Canada (1), and preliminary evidence that it may be possible to identify those women most at risk of doing poorly (15). In this paper we describe the incidence and pattern of adverse maternal and perinatal outcomes prior to and since introducing the guidelines.

2.1 Materials and Methods

From the previous retrospective study (15), we identified those cases who had been cared for at BC Women’s, January 2000 to December 2001. The criteria for inclusion in that study were admitted women with pre-eclampsia, the haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, or eclampsia. The same criteria were used for the prospective part of the study published here, although the guidelines cover all women with either hypertension in pregnancy or gestational proteinuria or both.
In this context, pre-eclampsia was defined as at least two of the following: 1) hypertension (systolic blood pressure of 140 mmHg or greater and/or diastolic blood pressure 90 mmHg or greater, taken twice more than 4 hours apart) after 20 weeks of gestation, 2) proteinuria defined as 0.3g/d or more or 2+ or more dipstick proteinuria after 20 weeks of gestation, 3) non-hypertensive and non-proteinuric HELLP syndrome, using Sibai's criteria (23), or 4) an isolated eclamptic seizure without preceding hypertension or proteinuria, using the British Eclampsia Survey Team (BEST) criteria to define eclampsia (24).

These guidelines were developed as a minimum standard. The timing of the investigations was at least as frequently as the day of admission, admission day +1, every Monday/Thursday (ante- and postpartum), day of delivery, and delivery day +1. Additional clinical, laboratory, and ultrasound evaluations were performed whenever considered necessary or prudent by providers. There is no policy of mandatory subspecialty consultation.

In addition to routine measurement of maternal blood pressure, the investigations included the following:

1. Hematology: full blood screen, international normalized ratio (INR), activated partial thromboplastin time (APTT), and fibrinogen.

2. Renal: urea, creatinine, electrolytes, uric acid, and dipstick. While other testing occurred twice weekly, urine was also assessed by 24-hour urine for protein and creatinine clearance (on admission and once weekly thereafter [every Sunday/Monday]).
3. Hepatic: aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), bilirubin, albumin (plasma), and random glucose.

4. Respiratory: pulse oximetry.

5. Fetal surveillance (antenatally only): cardiotocography (CTG; daily), ultrasound for assessment of fetal weight (every 14 days), and amniotic fluid volume and umbilical artery Doppler (twice weekly).

These guidelines were introduced into practice in September 2003 through the North American practice of standing orders. Standing orders are pre-printed forms used to standardize management to improve outcomes. The use of the standing orders was monitored each weekday by two of us (J.M. and B.B.), and those practitioners not using the orders were contacted to request their use. Using a pre-/post-intervention study design, we examined the influence of introducing the guidelines on the incidence of the combined adverse maternal outcome.

The combined outcome was maternal death or one or more of hepatic failure, haematoma, or rupture, Glasgow coma score less than 13, stroke, two or more seizures, cortical blindness, need for positive inotrope support, myocardial infarction, infusion of any third antihypertensive, renal dialysis, renal transplantation, 50% or more FIO₂ for more than 1 hour, intubation, or transfusion of 10 or more units of blood products (15). We also assessed a combined adverse perinatal outcome (Delphic consensus): perinatal or infant mortality, bronchopulmonary dysplasia, necrotizing enterocolitis, grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, or stage 3 - 5 retinopathy of prematurity (15). More details of methodologies utilized are provided in Appendix A.
Specifically, comparisons were made based on the incidence among 295 women from the feasibility study of January 2000 to December 2001 (as pre-intervention) and 405 women with completed charts from the post-intervention period of September 1, 2003 to February 28, 2007. Because the incidence was uncommon (particularly in the post-intervention period), statistical analysis of rates and ratios were carried out by assessing Fisher exact test and odds ratio, using Prism 4.0 (GraphPad, San Diego, CA, USA). For continuous variables (demographics), Student t-test was used, unless otherwise stated. Significance was set at p<0.05. The study was approved by the University of British Columbia Clinical Research Ethics Board and Children’s and Women’s Health Centre of British Columbia Research Review Committee (Appendix C).

2.2 Results

Of the 594 women included in the retrospective study (15), 295 were cared for at BC Women’s; of these, 15 women (5.1%) developed the outcome. The post-intervention cohort includes data from 405 women, of whom one was a postpartum transfer accompanying an infant admitted for neonatal intensive care.

Table 2.1 presents the clinical characteristics of the women in both cohorts. Initially, use of the standing orders for eligible antepartum women was 42%. For the final 15 months of the study period, the use remained consistently above 92% for antepartum women. Of the 404 women admitted antepartum for whom the orders were used, the minimum frequency of surveillance set by the standing orders was not met in 37 (9.2%) women, with 158 (39.1%) and 209 (51.7%) receiving surveillance either matching or exceeding the minimum frequency, respectively.
At all time periods, postpartum orders use remained about 10% lower than for the antepartum orders. The women in the post-intervention cohort were at least as unwell with pre-eclampsia (in terms of objective blood pressure, renal and hepatic markers of disease severity) as the women in the pre-intervention cohort. Women in the post-intervention cohort were also admitted at an earlier gestational age, were more likely to carry a multiple pregnancy, and more likely to receive antihypertensive medications than women in the pre-intervention cohort. Expectant management was more commonly used post-intervention, as reflected in the increased admission-to-delivery interval for the whole post-intervention cohort.

For women admitted before 34\textsuperscript{+0} weeks of gestation (when expectant management could be anticipated), the median admission-to-delivery interval was two days greater for the post-intervention (128/405) than for the pre-intervention (99/295) cohort (4 days, interquartile range 2-9, compared with 2 days, interquartile range 1-3, respectively; Mann-Whitney U p<0.001).

Since the introduction of the standing orders, the incidence of the combined adverse maternal outcome fell from 5.1% (15/295) to 0.7% (3/405); Fisher exact test, p<0.001; odds ratio 0.14 (95% confidence interval 0.04-0.49), with a power of 0.89 (Table 2.2). The combined adverse perinatal outcome did not differ between cohorts, but there was a trend to improved outcomes in the post-intervention period (Table 2.3).

### 2.3 Discussion

Introducing standing orders was associated with a reduced incidence of adverse maternal outcomes. This effect was greater than we had anticipated, and than could have
been expected from the experience of others (6). The women in the post-intervention cohort were certainly not at lower risk than were those in the pre-intervention cohort; they had higher admission blood pressure and heavier admission dipstick proteinuria, and had earlier-onset disease (15). Twenty-four hour urines were collected in less than 60% of both cohorts; therefore, we cannot comment on the comparability of fully assessed proteinuria. We believe that the failure to routinely complete 24-hour collections was due to the fact that most cases of pre-eclampsia arise at term, and those women are generally admitted for delivery, and 24-hour urine collection is generally not practicable under those circumstances, even in a tertiary health sciences center. The maternal age differences and rising rates of multiple births (primarily through assisted reproductive techniques) observed between the cohorts reflect the changing maternity demographics seen in British Columbia (25).

We recognize that combined adverse outcomes always reflect a spectrum of adversity (26). For example, is the decision to use a third antihypertensive equivalent to the occurrence of stroke? This combined adverse maternal outcome was agreed upon by a Delphic consensus of internationally recognized experts in the field (15). We believe that it is unusual for women to receive three parenteral antihypertensives (indeed, only 3 [0.43%] of the total 700 women did so). In this institution, this would reflect perceived clinical failure by the treating physicians (obstetrician, obstetric internist and/or obstetric anesthesiologist) of both intravenous labetalol and hydralazine, precipitating the use of nitroprusside. We were not prescriptive of clinical practice, and no set guidelines were in place to guide the timing of the use of a third parenteral agent.
The improvements in outcome came during a phase of increasing institutional acceptance of expectant management of pre-eclampsia remote from term (27). It might have been anticipated that increasing use of expectant management would be associated with increases, rather than decreases, in maternal morbidity (28), because most practitioners await deteriorating maternal condition to precipitate the decision to deliver. We identified that women in the post-intervention cohort admitted at less than 34+0 weeks gestation had longer admission-to-delivery intervals than did those in the pre-intervention cohort, confirming our impression that local practice had changed. There was no change in adverse perinatal outcomes in the post-intervention cohort (indeed the incidence of necrotizing enterocolitis was lower). Although there is the potential for a type II error, the trend towards a decrease in adverse perinatal outcome occurred in the post-intervention cohort in which there was a lower gestational age at which the women were both admitted and delivered.

We were fortunate that the process of introducing a standardized pattern of assessment and surveillance for women admitted to a tertiary perinatal unit with either suspected or confirmed pre-eclampsia had the full support of the hospital administration, and occurred through a stepwise process of feasibility study (15), education (of medical, nursing, administration, and clerical colleagues), ongoing surveillance of implementation, and review of outcomes.

It is possible that the apparent success of introducing the standing orders may have accrued from the fact that they were not accompanied by management guidelines from the outset; a group of competent providers, when asked to collect data did not feel intimidated but did intervene more appropriately when presented with a standardized data
set. In comparison with the findings of Foy et al (6), who found that the introduction of a complex set of guidelines was not effective in either altering practice or standardizing care, we chose to address a single element of the management of women admitted with the hypertensive disorders of pregnancy, namely their laboratory assessment and ongoing surveillance. The Yorkshire guidelines, which were introduced to guide the management of, rather than surveillance of, women with severe pre-eclampsia, have also been associated with reduced levels of maternal morbidity and rates of both between-hospital transfers and intensive care admissions (29). Our experience with the standing orders is complementary to that of the Yorkshire group because our center is currently introducing management guidelines to the province of British Columbia in the context of a funded health services research project that will assess the manner of guideline introduction and the impact of those guidelines on outcomes across the province. These guidelines are based on those developed and introduced so successfully in Yorkshire and the standing orders. We believe that taking iterative steps will advance the quality of care more effectively than would trying to address all issues with a single large, and overwhelming, document addressing all aspects of care.

It is unclear what elements of the standing orders may have contributed to the fall in adverse maternal outcomes, although some have been identified through the retrospective study (15) and by others (30). Certainly, before the introduction of the standing orders, the frequency and complexity of investigations varied between clinicians, as was predicted by our national review of practice (1). We recognize that the number of tests in the current regimen is greater than that which is standard in most units. The identification of those elements of this standardized approach that are truly
predictive of adverse maternal outcomes is occurring through an international study to
develop an outcome prediction model for women with pre-eclampsia, the PIERS (Pre-
eclampsia Integrated Estimate of RiSk) model. Once the PIERS model has been
established, then a reduced list of investigations will be suggested to replace the current
list that we recognize is probably overly thorough and, therefore, expensive.

The pattern of investigations has standardized the approach within our unit. The
choice of follow-up surveillance testing being on Mondays and Thursdays was made to
improve the timing the delivery of infants away from times of reduced pediatric staffing,
especially for those remote from term (31). Of course, some or all of these investigations
were performed at other additional times, at the discretion of the attending doctor or
midwife; the influence of these ‘unscheduled’ tests in the management of women with
pre-eclampsia is a secondary outcome for the PIERS project.

A study limitation is that we do not have data on the eligible women who did not
receive care using the standing orders during the post-intervention phase of the study. In
part, this is because we were aware of some women who were admitted with very severe
pre-eclampsia and some end organ complications that evolved to become severe enough
to fulfill the combined adverse maternal outcome. The physicians in these cases chose to
write their own orders that almost matched the standing orders, but not fully. Therefore,
we would have overly biased the analyses in favor of the standing orders.

In addition, we were underpowered to perform logistic regression analyses to
determine the magnitude of any possible independent effect of the standing orders in
influencing the change in outcomes. While we have data on antihypertensive drug use in
the retrospective cohort, we do not know the number of agents and duration of their use.
Similarly, we do not have data on the rate of Cesarean delivery in the pre-intervention cohort.

We recognize that the use of a pre-intervention and post-intervention design is another significant limitation to this study. A better approach may have been to have randomized women to the use of guidelines or not. However, this methodology could not have been blinded, and we were concerned that the Hawthorne effect (32) would have been profound as women not randomized to the guidelines may have received significantly more detailed care than did those women who received care in our unit before the introduction of the guidelines. We are also reassured through the knowledge that the women in the post-intervention cohort were at a comparable, if not greater, baseline risk on admission, and received a greater degree of expectant management (Table 2.1).

Therefore, we conclude that carefully introducing and implementing standardized initial assessment and ongoing surveillance of women admitted to our hospital with pre-eclampsia has been associated with a reduced incidence of adverse maternal outcomes.
### 2.4 Tables and Figures

#### Table 2.1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-intervention (n=295)</th>
<th>Post-intervention (n=405)</th>
<th>P (Fisher or t Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at EDD (years)</td>
<td>30.7 (30.0, 31.4)</td>
<td>32.5 (31.9, 33.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age on admission (weeks)</td>
<td>36.0 (35.4, 36.5)</td>
<td>35.1 (34.6, 35.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Early onset disease (admission before 34\textsuperscript{th} weeks of gestation)</td>
<td>99 (33.6)</td>
<td>128 (31.6)</td>
<td>0.624</td>
</tr>
<tr>
<td>Multiple pregnancy (triplets: one set pre-intervention, two sets post-intervention)</td>
<td>4 (1.4)</td>
<td>49 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parity: 1 or greater</td>
<td>86 (29.2)</td>
<td>104 (25.7)</td>
<td>0.344</td>
</tr>
<tr>
<td>Smoking</td>
<td>26 (8.8)</td>
<td>31 (7.7)</td>
<td>0.579</td>
</tr>
<tr>
<td>Corticosteroid administration</td>
<td>107 (36.3)</td>
<td>143 (35.3)</td>
<td>0.811</td>
</tr>
<tr>
<td>Antihypertensive use</td>
<td>144 (48.8)</td>
<td>295 (72.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Magnesium sulfate use</td>
<td>152 (51.5)</td>
<td>186 (45.9)</td>
<td>0.147</td>
</tr>
<tr>
<td>Blood pressure (mmHg) (highest in 1\textsuperscript{st} 24 h of admission)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure*</td>
<td>121.5 (120.0, 123.0)</td>
<td>125.1 (123.9, 126.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>160.4 (158.2, 162.6)</td>
<td>168.8 (167.0, 170.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>102.8 (101.5, 104.1)</td>
<td>105.5 (104.5, 106.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dipstick proteinuria (+) (highest in 1\textsuperscript{st} 24 h of admission)</td>
<td>1.55 (1.39, 1.71)</td>
<td>2.49 (2.37, 2.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (Units/L) (highest in 1\textsuperscript{st} 24 h of admission)</td>
<td>78.8 (49.1, 108.4)</td>
<td>76.3 (55.7, 96.9)</td>
<td>0.886</td>
</tr>
<tr>
<td>Platelets (x10\textsuperscript{9}/L) (lowest in 1\textsuperscript{st} 24 h of admission)</td>
<td>189 (180, 198)</td>
<td>191 (183, 198)</td>
<td>0.356</td>
</tr>
<tr>
<td>Admission to delivery interval (days) for admissions at all gestational ages</td>
<td>2.35 (1.73, 2.97)</td>
<td>3.76 (3.04, 4.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission to delivery interval (days) for women with early onset disease (admissions before 34\textsuperscript{th} weeks of gestation)</td>
<td>4.68 (2.96, 6.41)</td>
<td>7.90 (5.92, 9.88)</td>
<td>0.020</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>36.3 (35.8, 36.8)</td>
<td>35.6 (35.2, 36.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birthweight (g) †</td>
<td>2621 (2499, 2743)</td>
<td>2415 (2318, 2512)</td>
<td>0.009</td>
</tr>
<tr>
<td>SGA‡ (birth weight &lt; third percentile)†</td>
<td>16 (5.4)</td>
<td>34 (8.4)</td>
<td>0.140</td>
</tr>
</tbody>
</table>

EDD, estimated date of delivery; AST, aspartate transaminase; SGA, small for gestational age.

Data are expressed as mean (95% confidence interval) or n (%).

*Mean arterial pressure is diastolic blood pressure + (pulse pressure/3).

†Birth weight assessed was that of the smallest fetus in a multiple pregnancy.

‡For SGA, the pregnancy was deemed to have achieved the outcome if any one fetus was born at less than the third weight percentile for gestational age and gender.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention (n=295)</th>
<th>Post-intervention (n=405)</th>
<th>$P$ Fisher Exact</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more of maternal mortality or morbidity*</td>
<td>15 (5.1) 3 (0.7)</td>
<td>3 (0.7)</td>
<td>&lt;0.001</td>
<td>0.14 (0.04, 0.49)</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maternal morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>0.177</td>
<td>0.14 (0.01, 3.03)</td>
</tr>
<tr>
<td>Haematoma/Rupture</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow coma score &lt;13</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>0.421</td>
<td>0.24 (0.01, 5.97)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>0.177</td>
<td>0.14 (0.01, 3.03)</td>
</tr>
<tr>
<td>Cortical blindness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥2 seizures of eclampsia</td>
<td>3 (1.0)</td>
<td>0 (0)</td>
<td>0.074</td>
<td>0.10 (0.01, 2.00)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive inotrope support</td>
<td>1 (0.3)</td>
<td>1 (0.2)</td>
<td>0.421</td>
<td>0.02 (0.01, 5.97)</td>
</tr>
<tr>
<td>Infusion of a third parenteral antihypertensive</td>
<td>3 (1.0)</td>
<td>0 (0)</td>
<td>0.074</td>
<td>0.10 (0.01, 2.00)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>0.177</td>
<td>0.14 (0.01, 3.03)</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transplantation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requirement of 50% or more FiO₂ for more than 1 h</td>
<td>0 (0)</td>
<td>2 (0.5)</td>
<td>0.512</td>
<td>3.66 (0.18, 76.61)</td>
</tr>
<tr>
<td>Intubation (other than for Cesarean delivery)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>1.000</td>
<td>2.19 (0.09, 54.03)</td>
</tr>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion of 10 Units or more of blood products</td>
<td>7 (2.4)</td>
<td>1 (0.2)</td>
<td>0.012</td>
<td>0.10 (0.01, 0.83)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; FiO₂, fraction of inspired oxygen.

Data are expressed as n (%).

*Some women achieved more than one outcome (one woman achieved five).
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention (n=295)*</th>
<th>Post-intervention (n=405)*</th>
<th>$P$ Fisher Exact</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more of perinatal mortality or morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillbirth</td>
<td>26 (8.8)</td>
<td>24 (5.9)</td>
<td>0.181</td>
<td>0.65 (0.37, 1.16)</td>
</tr>
<tr>
<td>Neonatal mortality†</td>
<td>5 (1.7)</td>
<td>10 (2.5)</td>
<td>0.602</td>
<td>1.47 (0.50, 4.34)</td>
</tr>
<tr>
<td>Perinatal morbidities†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPD</td>
<td>12 (4.1)</td>
<td>9 (2.3)</td>
<td>0.183</td>
<td>0.54 (0.22, 1.30)</td>
</tr>
<tr>
<td>IVH (grade 3 or 4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>cPVL</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>0.179</td>
<td>0.15 (0.01, 3.05)</td>
</tr>
<tr>
<td>NEC</td>
<td>7 (2.4)</td>
<td>2 (0.5)</td>
<td>0.041</td>
<td>0.21 (0.04, 0.998)</td>
</tr>
<tr>
<td>ROP (grade 4 or 5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; cPVL, cystic periventricular leukomalacia; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity.

Data are expressed as n (%).

*For all adverse outcomes, the pregnancy was deemed to have achieved the outcome if any one fetus did so.

† Of liveborn infants.
2.5 References


(13) Smith S. Successful outcomes with the h.e.a.l. program. Ostomy Wound Manage 2006 Mar;52(3):40-2, 44, 46.


40


CHAPTER 3

Current CHS and NHBPEP Criteria for Severe Pre-eclampsia do not Uniformly Predict Adverse Maternal or Perinatal Outcomes

Pre-eclampsia is a leading cause of maternal mortality in the developed and developing worlds (1-6). Current classification systems are based on knowledge about the clinical picture and pathogenesis of pre-eclampsia, which is classically defined as gestational hypertension and proteinuria, with severe pre-eclampsia having severe hypertension, heavy proteinuria, and/or other end-organ system involvement (7;8). Classification systems facilitate standardization of diagnostic definitions. In addition, by assessing measures of severity, these systems should also identify women and babies at greatest risk of adverse outcomes. If classification systems could assess likely morbidity, clinicians could determine whether or not to: wait for the maximal effect of antenatal corticosteroids for women remote from term, expectantly manage pre-eclampsia (particularly when women are remote from term), or transfer patient care (at any gestational age) to a higher-level institution or more skilled care-giver. Under these circumstances, classification systems would also aid researchers in identifying women at highest risk for both basic science and intervention studies.

At present, we do not know whether the published criteria for pre-eclampsia severity actually identify women (or babies) at highest risk of adverse outcomes.

Pre-eclampsia is a multi-system disorder akin to the Systemic Inflammatory Response Syndrome (SIRS) (9). In the setting of SIRS, a number of predictive tools have been developed to identify those patients at greatest risk for mortality. These tools include MODS (Multiple Organ Dysfunction Score) and the leading adult scoring tool, APACHE (Acute Physiology and Chronic Health Evaluation) (10). There is no such tool for women with pre-eclampsia. APACHE did not perform well in the prediction of maternal mortality among women with eclampsia who were admitted to ICU (11) and in addition, maternal mortality is rare in pre-eclampsia in the developed world.

The international PIERS project (Pre-eclampsia Integrated Estimate of RiSk) is designed to determine, for women admitted to hospital with pre-eclampsia, which of the maternal symptoms, maternal signs, maternal laboratory tests (to detect maternal morbidity), and/or tests of fetal well-being predict adverse maternal and/or perinatal outcome. This report describes our analysis, using PIERS data, of the association between adverse maternal or perinatal outcomes and the pre-eclampsia severity criteria published by the Canadian Hypertension Society (CHS) and the National Hypertension Blood Pressure Education Program Working Group on Hypertension in Pregnancy (NHBPEP, USA). As such, this paper aims to assess the validity of pre-eclampsia severity criteria as true predictors of adverse maternal and/or perinatal outcome.

### 3.1 Methods

PIERS is an international project that began in September 2003, and now runs in seven international sites (Vancouver, Sherbrooke, Kingston, and Ottawa, Canada; Christchurch, New Zealand; Leeds, UK; Perth, Australia [from July 2006]). All sites
have obtained approval for PIERS from the appropriate local Research Ethics Boards. At five of the six sites, PIERS is run as a continuous quality assurance project in which there are pre-printed ‘standing orders’ for the investigation and surveillance of women with pre-eclampsia and their babies. The local site co-coordinator reinforces use of these orders on a day-to-day, and care-giver to care-giver, basis.

Women are assessed for their eligibility for PIERS if they are admitted to hospital with gestational hypertension. Women could become eligible for PIERS during their admission. Inclusion criteria are: i) blood pressure (BP) ≥140/90mmHg (twice, ≥4hr apart, after 20 weeks’ gestation, by any method in hospital) and either proteinuria (of ≥2+ by dipstick, ≥0.3g/d by 24hr urine collection, or >30mg/mmol by spot urinary protein:creatinine ratio) or hyperuricaemia (greater than local upper limit of normal for non-pregnant individuals) (12), or ii) HELLP syndrome (haemolysis, elevated liver enzymes and low platelet syndrome) even in the absence of hypertension or proteinuria, or iii) superimposed pre-eclampsia, defined as pre-existing hypertension with accelerated hypertension [as diagnosed by the clinician, or defined as a systolic BP (sBP) ≥170mmHg or diastolic BP (dBP) ≥120mmHg], new proteinuria or new hyperuricaemia. This definition of pre-eclampsia was intended to reflect the spectrum of pre-eclampsia, and incorporate data justifying ongoing inclusion of hyperuricaemia in the definition (12). Women who have already achieved any component of the maternal outcome (e.g., eclampsia) are excluded from the dataset, as prediction of adverse maternal outcome is the primary objective of PIERS.

The methods by which the PIERS candidate predictor variables were chosen has been previously published (13). These predictors include pre-eclampsia severity criteria
published by the CHS and NHBPEP; when phrasing of the variables differed (e.g., frontal headache by CHS but persistent headache by NHBPEP criteria), the CHS definition was chosen. More details of methodologies utilized for the PIERS program of research as a whole are provided in Appendix A.

Analysis of the CHS and NHBPEP criteria are the focus of this paper. The Australasian (ASSHP) and International Societies for the Study of Hypertension in Pregnancy (ISSHP) do not define severe pre-eclampsia (14;15). An analysis of the recently published RCOG definition of severe pre-eclampsia could not be performed, as PIERS does not include three of the nine RCOG severity criteria (i.e., clonus, papilledema, and liver tenderness) (16).

3.1.1 Factors measured at presentation to ‘predict’ the severity of pre-eclampsia

Table 3.1 presents the CHS and NHBPEP pre-eclampsia severity predictors, made up of: i) feto-placental signs (e.g., oligohydramnios), ii) maternal symptoms (e.g., headache), signs (e.g., systolic BP ≥160mmHg), and laboratory abnormalities (e.g., low platelets), and iii) the maternal clinical diagnoses of eclampsia and pulmonary edema. Eclampsia (CHS and NHBPEP) and pulmonary edema (CHS) were not included as potential predictors of adverse outcomes as they are actually part of the combined adverse maternal outcome. The CHS definitions were used for headache (i.e., frontal rather than persistent) and abdominal pain (i.e., right upper quadrant rather than persistent epigastric). ‘Other cerebral disturbances’ (which was not defined by NHBPEP) and microangiopathic hemolytic anemia (which is not in the PIERS dataset) could not be evaluated. The different definitions of severe hypertension (i.e., dBP >110mmHg by
CHS, vs. dBP ≥110mmHg or sBP ≥160mmHg by NHBPEP) and elevated liver enzymes (AST, ALT or LDH by CHS, vs. AST or ALT and LDH considered separately by NHBPEP) were evaluated. Neither the CHS nor the NHBPEP criteria include assessment of fetal heart rate and variability.

The CHS and NHBPEP severity predictors were collected within 48hr of eligibility. If absent, the ‘last observation carried forward’ method was used for results performed within two weeks of eligibility (17;18).

3.1.2 Factors used to define adverse maternal and perinatal outcomes

The components of the maternal and perinatal outcomes were finalised by international experts (using Delphic methods as previously published) (13), and modified at the 2004 PIERS Investigators’ meeting to reflect some other uncommon, less severe morbidities that are nevertheless dangerous in women with pre-eclampsia.

The combined adverse maternal outcome includes maternal mortality and serious maternal morbidity (as further defined in Appendix A): hepatic dysfunction, haematoma or rupture; eclampsia, Glasgow coma score <13; stroke or reversible neurological deficit; cortical blindness or retinal detachment; need for positive inotropic support; infusion of a third parenteral antihypertensive; myocardial ischemia/infarction; acute renal failure, dialysis, pulmonary oedema, requirement ≥50% FiO₂ >1hr; intubations (other than for Caesarean section); and transfusion of any blood product. The components are clinically relevant as they are worthy of avoidance, even in the face of extreme prematurely.

The combined adverse perinatal outcome includes perinatal or infant mortality, bronchopulmonary dysplasia (BPD), grade III or IV intraventricular haemorrhage (IVH),
cystic periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), or retinopathy of prematurity (ROP) (stage 3-5). Definitions for each outcome component are provided in Appendix A.

3.1.3 Statistical Analyses

We sought to predict any of the defined adverse maternal or perinatal outcomes at any time after eligibility. The number of women with data for each of the CHS and NHBPEP severity predictors, and the prevalence of those variables, was determined. Those variables that were available for at least 80% of the PIERS cohort were included in a univariable analysis (Fisher’s exact test), examining the relationship between each variable and any adverse maternal or perinatal outcome. Due to multiple comparisons, a p value <0.01 was considered to be statistically significant.

3.2 Results

From September, 2003 until August 23, 2006, 737 women were included in the PIERS project from six international sites (Vancouver, Sherbrooke, Kingston, and Ottawa, Canada; Christchurch, New Zealand; Leeds, UK).

Table 3.2 presents the baseline characteristics of the PIERS cohort of 737 women admitted to hospital with pre-eclampsia. Most women were nulliparous at the time of admission (or eligibility), non-smokers, and were carrying singletons. Women most commonly met eligibility criteria due to hypertension and proteinuria at ≥34 weeks; 445 women had ≥2+ proteinuria by dipstick, but another 19 women had ≤1+ dipstick proteinuria with either 0.3g/d proteinuria by 24hr collection, or >30mg/mmol by spot
urinary protein:creatinine ratio. Approximately half of women were on antihypertensive therapy with BP values greater than 160mmHg systolic and 100mmHg diastolic. The median pregnancy prolongation was two days.

Table 3.3 presents the incidence of the adverse maternal and perinatal outcomes in the PIERS cohort. Overall, 72 (9.8%) of women experienced maternal morbidity. These outcomes occurred antenatally in 49 (68.1%) of women and postnatally in 23 (31.9%). Almost all (65/72) outcomes occurred between admission and day two postpartum. Most commonly, women developed pulmonary edema (5.0%) or required transfusion of blood product (4.3%). Reliable information on fluid balance was not available from the patient record. Overall, 38 (5.2%) of fetuses/babies had an adverse perinatal outcome. The most common of these were stillbirth (1.4%), BPD (1.9%), and NEC (1.2%).

Tables 3.4a and 3.4b present, for each of the CHS and NHBPEP severity criteria (respectively), the prevalence of the predictor factors, and association by univariable analysis with any adverse maternal or perinatal outcome. Variables that were excluded because they were available for <80% of the PIERS cohort were: proteinuria ≥2g/d (NHBPEP) and oliguria, proteinuria >3/d, IUGR, oligohydramnios, absent or reversed end-diastolic flow by umbilical artery Doppler velocimetry (all CHS). Even if a 24hr urinary protein or a protein:creatinine ratio result (both of which are in the PIERS standing orders) were accepted for quantification of proteinuria, the tests were performed in 558 (75.7%) of women, too few to be included in the univariable analysis.

The following variables at entry were associated, at the p<0.01 level, with adverse maternal outcome: chest pain/dyspnoea (CHS), platelets <100x10^9/L (CHS and
NHBPEP), elevated liver enzymes (CHS), increased AST or ALT (NHBPEP), increased LDH (NHBPEP), HELLP syndrome (CHS), and creatinine >110µM (NHBPEP).

The following variables at entry were associated, at the p<0.01 level, with adverse perinatal outcome: dBP >110mmHg (CHS) and suspected abruption (CHS).

3.3 Discussion

The PIERS project aims to identify, for women admitted to hospital with pre-eclampsia, which maternal and fetal variables can identify women and babies at highest risk of adverse outcomes. The analysis presented here used the PIERS dataset to examine the predictive ability of published Canadian and American pre-eclampsia severity criteria. There are three major conclusions that can be drawn.

First, many of the severity criteria proposed by the CHS and/or NHBPEP were not consistently documented or performed and therefore, were not able to be examined for their association with adverse maternal or perinatal outcomes. No fetal variable (i.e., IUGR, oligohydramnios, and abnormal umbilical Doppler velocimetry) was sufficiently available at eligibility. Therefore, our analysis was restricted to maternal variables and their association with either adverse maternal or perinatal outcomes.

PIERS is a continuous quality improvement project, with ongoing audit and reinforcement of the use of pre-printed standing orders, so it is unlikely that variables missing in the PIERS data set would be performed in routine clinical practice. Of note, 24hr urinary protein was performed in only 47% of women, and quantification by spot protein:creatinine ratio in another 29%. This may be because many practitioners cancel orders for proteinuria quantification if induction of labour is planned. One could argue,
therefore, that proteinuria quantification (by 24hr urine collection or by spot protein:creatinine ratio) should not be included as a severity criterion for pre-eclampsia because it does not satisfy all requirements set out by Richardson for predictor variables (i.e., it is not obtained frequently enough) (19). Although dipstick proteinuria has poor sensitivity and specificity for quantification of urinary protein when compared with the 24hr urine collection, urinary dipstick proteinuria was sufficiently available to be considered for its association with adverse outcomes, but was not significant as defined categorically as per NHBPEP criteria (Table 3.4b).

Second, there are maternal variables that may predict only adverse maternal outcomes (e.g., chest pain/dyspnoea) and those that may predict only adverse perinatal outcomes (e.g., dBP >110mmHg or suspected placental abruption). Such a distinction has not been previously specified in pre-eclampsia classification criteria, but may be of relevance to particular patients and in particular settings (e.g., developing world). The optimal definitions of pre-eclampsia severity criteria must be determined. For example, ‘elevated liver enzymes’ was defined in three ways as: increased AST, ALT or LDH (by CHS), increased LDH (NHBPEP), or increased AST or ALT (NHBPEP). Although any of these definitions defines a predictor that is strongly associated with adverse maternal outcome, the association with perinatal outcome was more variable.

Most variables do not appear to be related at all to adverse maternal or perinatal outcomes. Visual disturbances is a notable example of this, particularly given that it is listed as a potential indication for delivery in pre-eclampsia remote from term (20), a recommendation that was endorsed by 79% of obstetricians in a national Canadian survey (21).
Third, there are limitations to both the CHS and NHBPEP pre-eclampsia severity criteria, as named and defined. There are potentially important omissions in the criteria, such as gestational age at diagnosis of hypertension. Also, all variables are treated dichotomously. Arbitrary cut-offs have been chosen without information about the relationship of these cut-offs to adverse outcomes. This may explain why some (e.g., dipstick proteinuria) do not appear to be related, or related strongly, to adverse outcomes, despite older literature suggesting the contrary is true (22). In the final PIERS analysis, variables will be analysed continuously (e.g., BP) or categorically (e.g., symptoms or dipstick proteinuria), as appropriate, to take full advantage of their potential relationship with adverse outcomes.

Finally, there are limitations to the current analysis. We arbitrarily chose CHS definitions for certain variables (e.g., headache and abdominal pain) because it would be too onerous to collect data using more than one definition. There was potential for inaccurate measurement of BP, which could influence the diagnosis of hypertension (most likely if BP were only minimally elevated) or severe hypertension. However, pre-eclampsia severity criteria, if predictive of adverse outcomes, should do so based on clinical BP measurements. Also, the predictive value of severe hypertension may have been mitigated by antihypertensive therapy, which was not accounted for in this analysis.

3.4 Conclusion

Most of the current Canadian and American pre-eclampsia severity criteria do not predict adverse maternal or perinatal outcomes as defined herein. These data suggest that pre-eclampsia severity criteria should not include quantification of urinary protein and
ultrasonographic tests of fetal well-being, unless they are performed routinely, because in current clinical practice, it seems that they are not sufficiently available to be evaluated as predictors of adverse outcomes. PIERS will evaluate all variables simultaneously for their incremental ability to predict adverse maternal and perinatal outcomes.

What is appropriate at this time is caution about firstly, the usefulness of current pre-eclampsia severity criteria, particularly as indications for delivery of pregnancies remote from term, and secondly, the premature abandonment of dipstick proteinuria before its validation against adverse maternal and perinatal outcomes.
### 3.5 Tables and Figures

#### Table 3.1: Canadian Hypertension Society (CHS) and National High Blood Pressure Education Program (NHBPEP) candidate predictors of severe pre-eclampsia*

<table>
<thead>
<tr>
<th></th>
<th>Canadian Hypertension Society Severity Criteria</th>
<th>NHBPEP Severity Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions*</td>
<td></td>
<td>Eclampsia*</td>
</tr>
<tr>
<td>Frontal headache</td>
<td></td>
<td>Persistent headache</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td></td>
<td>Visual or “other cerebral disturbances”</td>
</tr>
<tr>
<td><strong>Cardiorespiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain/dyspnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dBP &gt;110mmHg</td>
<td></td>
<td>sBP ≥160mmHg or dBP ≥110mmHg</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td>Creatinine &gt;110µM</td>
</tr>
<tr>
<td>Oliguria (&lt;500ml/d),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria &gt; 3g/d*</td>
<td></td>
<td>Proteinuria ≥2g/d (or ≥2+)</td>
</tr>
<tr>
<td><strong>Haematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt;100 x 10⁹/L</td>
<td></td>
<td>Platelet count &lt;100 x 10⁹/L</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AST ≥70 U/L, LDH ≥ 600U/L AND platelets &lt;100x10⁹/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent right upper quadrant pain</td>
<td></td>
<td>Persistent epigastric pain</td>
</tr>
<tr>
<td>Severe nausea and vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AST &gt;40U/L, ALT &gt;55U/L or LDH &gt;600U/L)</td>
<td></td>
<td>Increased AST and/or ALT</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td>Increased LDH (&gt;600U/L)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin &lt;18g/L*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected abruption†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUGR‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligohydramnios¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent or reversed umbilical arterial end-diastolic flow (Doppler)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The criteria shaded in gray were not included in the analysis. Convulsions and pulmonary edema were excluded as they are part of the PIERS adverse maternal outcome. “Other cerebral disturbances” and microangiopathic haemolytic anaemia were not part of the PIERS data set. All maternal symptoms were considered to be present if indicated as such in the medical record.

† Suspected abruptio placentae was defined in PIERS as abruption diagnosed clinically by abdominal pain or uterine contractions with one or more of: vaginal bleeding, intrauterine fetal death, or disseminated intravascular coagulation (DIC).

‡ IUGR was defined in PIERS as AC ≤10% centile for gestational age (23).

¶ Oligohydramnios was defined in PIERS as amniotic fluid index (AFI) <50mm for singletons, or deepest amniotic fluid pocket (DAP) <20mm for multiples.

AST (aspartate aminotransferase), ALT (alanine aminotransferase), CNS (central nervous system), dBP (diastolic blood pressure), HELLP syndrome (haemolysis, elevated liver enzymes, low platelets), IUGR (intrauterine growth restriction), LDH (lactate dehydrogenase), NHBPEP (National High Blood Pressure Education Program, USA), sBP (systolic blood pressure).
<table>
<thead>
<tr>
<th>Table 3.2: Baseline characteristics of 737 women at entry into PIERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal age</strong> (years)</td>
</tr>
<tr>
<td><strong>Gestational age</strong> (weeks)</td>
</tr>
<tr>
<td>&lt;34 weeks</td>
</tr>
<tr>
<td><strong>Multiple pregnancy</strong></td>
</tr>
<tr>
<td><strong>Parity ≥ 1</strong></td>
</tr>
<tr>
<td><strong>Pre-eclampsia description</strong></td>
</tr>
<tr>
<td>Hypertension and proteinuria</td>
</tr>
<tr>
<td>Hypertension and hyperuricaemia</td>
</tr>
<tr>
<td>HELLP without hypertension or proteinuria</td>
</tr>
<tr>
<td>Superimposed pre-eclampsia</td>
</tr>
<tr>
<td><strong>On anti-hypertensive treatment</strong></td>
</tr>
<tr>
<td><strong>Peak blood pressure</strong> (mmHg)</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>Systolic BP</td>
</tr>
<tr>
<td>Diastolic BP</td>
</tr>
<tr>
<td><strong>Worst dipstick proteinuria</strong></td>
</tr>
<tr>
<td>Negative/trace</td>
</tr>
<tr>
<td>1+</td>
</tr>
<tr>
<td>2+</td>
</tr>
<tr>
<td>3+</td>
</tr>
<tr>
<td>4+</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
</tr>
<tr>
<td><strong>Days until delivery</strong></td>
</tr>
<tr>
<td><strong>Gestational age at delivery</strong> (wk)</td>
</tr>
<tr>
<td><strong>Birthweight</strong> (g)</td>
</tr>
<tr>
<td><strong>Birthweight &lt;3rd centile age</strong> (N babies) (24)</td>
</tr>
</tbody>
</table>

Data expressed as n (%), mean ± SD, or median [interquartile range].
* Within 1 day of eligibility.
BP (blood pressure).
## Table 3.3: Adverse maternal and perinatal outcomes*

<table>
<thead>
<tr>
<th>One or more of maternal morbidity or mortality, n (%):</th>
<th>72 (9.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal death</td>
<td>0</td>
</tr>
</tbody>
</table>

### Maternal morbidities:

#### Central nervous system
- Eclampsia (≥1) 3
- Glasgow coma score <13 1
- Stroke or reversible neurological deficit 1
- Cortical blindness or retinal detachment 0

#### Cardiorespiratory
- Positive inotropic support 0
- Infusion of a 3rd parenteral antihypertensive 0
- Myocardial ischemia/infarction 0

#### Haematological
- Transfusion of any blood product 32

#### Hepatic
- Dysfunction 7
- Haematoma/rupture 0

#### Renal
- Acute renal failure 1
- Dialysis 0

#### Respiratory
- Pulmonary edema 37
- Requirement of ≥50% FiO₂ for >1 hr 9
- Intubation 3

### One or more of perinatal mortality, infant mortality or morbidity*, n (%):

<table>
<thead>
<tr>
<th></th>
<th>38 (5.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>10</td>
</tr>
<tr>
<td>Neonatal or infant death</td>
<td>8</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>14</td>
</tr>
<tr>
<td>Intraventricular haemorrhage grade III or IV</td>
<td>2</td>
</tr>
<tr>
<td>Cystic periventricular leukomalacia</td>
<td>0</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>9</td>
</tr>
<tr>
<td>Retinopathy of prematurity (stage 3-5)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Definitions are presented in Appendix A. These are not mutually exclusive, as some women suffered more than one outcome. FiO₂ (fractional inspired oxygen tension).
Table 3.4a: Canadian Hypertension Society (CHS) severity criteria and their relationship with adverse maternal and perinatal outcome*

<table>
<thead>
<tr>
<th>Body System</th>
<th>CHS pre-eclampsia severity criteria*</th>
<th>Women with predictor recorded as present or absent n (%)</th>
<th>Women with data with predictor present n (%)</th>
<th>Association with any adverse maternal outcome (2-sided p)†</th>
<th>Association with any adverse perinatal outcome (2-sided p)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Eclampsia‡</td>
<td>Frontal headache</td>
<td>737 (100%)</td>
<td>220 (29.9%)</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual disturbances</td>
<td>737 (100%)</td>
<td>134 (18.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chest pain or dyspnoea</td>
<td>737 (100%)</td>
<td>38 (5.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dBP &gt;110mmHg</td>
<td>727 (98.6%)</td>
<td>132 (18.2%)</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Renal</td>
<td>Oliguria (&lt;500mL/d)</td>
<td></td>
<td>440 (59.7%)</td>
<td>82 (18.6%)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td></td>
<td>Proteinuria &gt;3g/d</td>
<td></td>
<td>347 (47.1%)</td>
<td>74 (21.3%)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td>Haematology</td>
<td>Platelets &lt;100 x 10⁹/L</td>
<td></td>
<td>735 (99.7%)</td>
<td>53 (7.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>HELLP syndrome</td>
<td></td>
<td>736 (99.9%)</td>
<td>32 (4.3%)</td>
<td>0.077</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Persistent right upper quadrant pain</td>
<td></td>
<td>737 (100%)</td>
<td>124 (16.8%)</td>
<td>0.066</td>
</tr>
<tr>
<td></td>
<td>Severe nausea and vomiting</td>
<td></td>
<td>737 (100%)</td>
<td>40 (5.4%)</td>
<td>0.099</td>
</tr>
<tr>
<td></td>
<td>Elevated liver enzymes</td>
<td></td>
<td>737 (100%)</td>
<td>352 (47.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>Serum albumin &lt;18g/L</td>
<td></td>
<td>652 (88.5%)</td>
<td>11 (1.7%)</td>
<td>0.328</td>
</tr>
<tr>
<td></td>
<td>Suspected abruption</td>
<td></td>
<td>734 (99.6%)</td>
<td>21 (2.9%)</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>IUGR</td>
<td></td>
<td>380 (51.6%)</td>
<td>137 (36.1%)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td></td>
<td>Oligohydramnios</td>
<td></td>
<td>411 (55.8%)</td>
<td>27 (6.6%)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td></td>
<td>Absent or reversed umbilical</td>
<td></td>
<td>367 (49.8%)</td>
<td>26 (7.1%)</td>
<td>Not analyzed</td>
</tr>
<tr>
<td></td>
<td>end-diastolic flow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Definitions of adverse outcomes are presented in Appendix A.
† By Fisher’s exact test. P values that are <0.10 level are italicized. P values that are <0.01 are also bolded.
‡ Eclampsia and pulmonary edema are excluded as they are part of the maternal outcome.

CHS (Canadian Hypertension Society), CNS (central nervous system), dBP (diastolic blood pressure), IUGR (intrauterine growth restriction)
Table 3.4b: National High Blood Pressure Education Program (NHBPEP) severity criteria and their relationship with adverse maternal and perinatal outcome*

<table>
<thead>
<tr>
<th>Body System</th>
<th>NHBPEP pre-eclampsia severity criteria</th>
<th>Women with predictor recorded as present or absent n (%)</th>
<th>Women with data with predictor present n (%)</th>
<th>Association with any adverse maternal outcome (2-sided p)†</th>
<th>Association with any adverse perinatal outcome (2-sided p)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Eclampsia‡</td>
<td>-------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Persistent headache</td>
<td>737 (100%)</td>
<td>220 (29.9%)</td>
<td>0.225</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Visual or “other cerebral disturbances”‡‡</td>
<td>737 (100%)</td>
<td>134 (18.2%)</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiorespiratory</td>
<td>sBP ≥160mmHg or dBP ≥110mmHg</td>
<td>737 (100%)</td>
<td>479 (65.0%)</td>
<td>0.300</td>
<td>0.035</td>
</tr>
<tr>
<td>Renal</td>
<td>Creatinine &gt;110µM</td>
<td>734 (99.6%)</td>
<td>18 (2.5%)</td>
<td>&lt;0.001</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Proteinuria ≥2g/d</td>
<td>347 (47.1%)</td>
<td>97 (28.0%)</td>
<td>Not analyzed</td>
<td>Not analyzed</td>
</tr>
<tr>
<td></td>
<td>Proteinuria of ≥2+</td>
<td>726 (98.5%)</td>
<td>445 (61.3%)</td>
<td>0.609</td>
<td>0.060</td>
</tr>
<tr>
<td>Haematology</td>
<td>Platelets &lt;100 x 10⁹/L</td>
<td>735 (99.7%)</td>
<td>53 (7.2%)</td>
<td>0.001</td>
<td>0.013</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Persistent epigastric pain</td>
<td>737 (100%)</td>
<td>124 (16.8%)</td>
<td>0.066</td>
<td>0.234</td>
</tr>
<tr>
<td></td>
<td>Increased AST and/or ALT</td>
<td>737 (100%)</td>
<td>183 (24.8%)</td>
<td>0.006</td>
<td>0.085</td>
</tr>
<tr>
<td></td>
<td>Increased LDH or microangiopathic</td>
<td>698 (94.7%)</td>
<td>292 (41.8%)</td>
<td>0.001</td>
<td>0.374</td>
</tr>
<tr>
<td></td>
<td>hemolytic anemia‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Definitions of adverse outcomes are presented in Appendix A.
† By Fisher’s exact test. P values that are <0.10 level are italicized. P values that are <0.01 are also bolded.
‡ The criteria shaded in grey were not included in the analysis. Eclampsia is excluded as it is part of the maternal outcome. “Other cerebral disturbances” and microangiopathic hemolytic anemia were not part of the PIERS data set.
CNS (central nervous system), dBP (diastolic blood pressure), IUGR (intrauterine growth restriction), sBP (systolic blood pressure)
3.6 References


CHAPTER 4

Predicting Adverse Maternal Outcomes in Pre-eclampsia:

The PIERS (Pre-eclampsia Integrated Estimate of Risk) Models –
Development and Initial Validation*

Pre-eclampsia, generally defined as proteinuric gestational hypertension, is more than hypertension alone (1); it is also a state of exaggerated systemic inflammation (2). Pre-eclampsia remains a leading direct cause of maternal morbidity and mortality worldwide (3;4). The WHO estimates that, globally, at least one woman dies every seven minutes from pre-eclampsia (4). In high income countries, this excess maternal morbidity and mortality relates to both uncontrolled hypertension and the pulmonary and hepatic consequences of systemic inflammation (5;6).

For pre-eclampsia arising remote from term, the goal of management is to improve maternal and perinatal outcomes through temporising and supportive measures, as the only cure is delivery of the placenta. 40% of women who present remote from term are eligible for expectant care (7). Historically, there has been concern that although temporising (so-called expectant) management reduces perinatal risks, the magnitude of maternal risk is unclear (8).

For pre-eclampsia at or near term, the benefits of expectant management are less clear. For these women, improvements in clinical outcomes may occur if, for example, clinicians were able to identify those women for whom it is either safe to transfer to

* A version of this chapter will be submitted for publication. Menzies J, Magee LA, Li J, Lin Y, Ansermino JM, Douglas MJ et al for the PIERS Study Group. Predicting adverse maternal outcomes in pre-eclampsia: the PIERS (Pre-eclampsia Integrated Estimate of Risk) models-development and initial validation.
optimal care settings or reasonable to initiate induction of labour. It is concern around maternal risk has caused experts to hesitate in recommending expectant management either at, near, or remote from term (9), as obstetricians tend to be maternal risk averse.

The best methods for monitoring pregnancies being managed expectantly or during induction of labour remain unclear. Current guidelines for the diagnosis and management of pre-eclampsia have primarily relied on expert opinion to advise practitioners on which maternal and fetal tests to perform, when to perform them, and when to intervene based on the results (10-13).

Ultimately, what is required is a validated outcome prediction model that allows clinicians to stratify maternal risk in real-time to advise clinical decision-making by women, their families, and their caregivers. Such a tool could identify women at the lowest risk of adverse maternal outcomes (as well as those at greatest risk), and guide care in terms of supporting expectant management both remote from term or at term during an induction of labour. Such a model would also i) improve understanding of the disease process (by comparing biomarker data with improved categorisation of subgroups associated with differential maternal risk); ii) improve the design and analysis of clinical trials (e.g., risk stratification); iii) assist outcome comparison between treatment groups in non-randomised studies, by adjusting for case mix; iv) define at-risk groups based on prognosis (14); and v) improve confidence amongst caregivers in a risk-averse environment.

Previous prediction modelling was not successful when designed to predict adverse outcomes occurring at any time throughout the subsequent clinical course of women with pre-eclampsia (15). This is likely to have been due to the variable post-
admission evolution of the condition. However, being able to predict adverse maternal outcomes within a time frame that would inform and guide clinical care (e.g., 48h - 7d) would improve the management of women admitted with pre-eclampsia and facilitate the better utilisation of resources.

In one tertiary obstetric centre, the provision of standardised antenatal and postnatal assessment and surveillance of pre-eclampsia with protocols, that recognise the systemic inflammatory model of pre-eclampsia (2;13), has been associated with reduced maternal morbidity (16). Using this standardised approach, we have developed and validated two pre-eclampsia outcome prediction models, the PIERS (Pre-eclampsia Integrated Estimate of RiSk) models; fullPIERS for use in well-resourced settings, and miniPIERS (a simplified symptom- and sign-based model) for use in rural, remote, and low and middle income country settings.

4.1 Methods

The PIERS models were developed and validated in a prospective, multicentre study of women who fulfilled a research definition of pre-eclampsia, and who were admitted to academic tertiary obstetric centres. The centres were: in Canada, British Columbia's Women's Hospital/University of British Columbia, Vancouver, BC; Kingston General Hospital/Queen's University, Kingston, ON, the Ottawa Hospital (General Campus)/University of Ottawa, Ottawa, ON; and centre hospitalier universitaire de Sherbrooke/Université de Sherbrooke, QC; in the UK, St James Hospital/University of Leeds, Leeds, Yorks; in New Zealand, Christchurch Women's Hospital/University of Otago, Christchurch; and, in Australia, King Edward Memorial Hospital for
Women/University of Western Australia, Subiaco, WA. All these centres have a general policy of expectant management of pre-eclampsia remote from term; this decision was made to maximise temporal exposure of the cohort to the natural history of the condition. Follow-up was achieved up to six weeks’ postpartum or ultimate hospital discharge (which ever was later) for both the women and their newborns.

In three sites, PIERS was conducted as a continuous quality improvement (CQI) project. In the other four sites, women were required to give informed consent to be enrolled in PIERS. These variations were in response to local Ethics Committee requirements. The CQI project entailed the introduction of predetermined guidelines for the initial assessment and ongoing surveillance of women admitted to hospital with suspected/confirmed pre-eclampsia. The details of these guidelines have been published elsewhere (13;16;17).

Women were included if they were admitted with pre-eclampsia, or developed pre-eclampsia following admission. Pre-eclampsia was defined as: i) blood pressure (BP) ≥140/90mmHg (at least one component twice, ≥4hr apart, after 20 weeks’ gestation, by any method in hospital) and either proteinuria (of ≥2+ by dipstick, ≥0.3g/d by 24hr urine collection, or ≥30mg/mmol by spot urinary protein:creatinine ratio) or hyperuricaemia (greater than local upper limit of normal for non-pregnant individuals) (5), or ii) HELLP syndrome (haemolysis, elevated liver enzymes and low platelet syndrome) even in the absence of hypertension or proteinuria (18), or iii) superimposed pre-eclampsia, defined as pre-existing hypertension with accelerated hypertension [as diagnosed by the clinician, defined as rapidly increasing requirements for antihypertensives, or defined as a systolic BP (sBP) >170mmHg or diastolic BP (dBP) >120mmHg], new proteinuria or new
hyperuricaemia. This definition, although differing from many international definitions (10;11) was chosen to reflect both the variable and multisystem nature of pre-eclampsia at presentation and the spectrum of women seen in clinical practice (19). Women were excluded if they were admitted in spontaneous labour or had achieved any component of the maternal outcome prior to either fulfilling the eligibility criteria or collection of the predictors, as prediction of adverse maternal outcome was the primary objective of PIERS.

The candidate maternal and fetal predictor variables were chosen to fulfil Richardson’s criteria, in that they are: (i) predictive (i.e., correlate with the outcome of interest); (ii) available; (iii) measurable; (iv) frequent; and (v) reliable (20). Symptoms, although difficult to quantify, were included for face validity, due to their inclusion in many classification systems used to denote severe disease (10-13;21), and limited data suggesting that they do predict adverse maternal outcomes in pre-eclampsia (22). Those tested in the modelling are listed in Table 4.1.

The components of the combined adverse maternal outcome are as listed: maternal mortality or one/more of the following serious maternal morbidities: hepatic dysfunction, haematoma or rupture; one or more seizures of eclampsia, Glasgow coma score <13; stroke; reversible ischaemic neurological deficit; transient ischaemic attack; posterior reversible encephalopathy; cortical blindness or retinal detachment; need for positive inotrope support; infusion of a third parenteral antihypertensive; myocardial ischaemia/infarction (symptoms, ECG changes [ST segment changes, Q waves], biochemical markers [troponin, CK-MB]), coronary artery intervention, or pathological findings); acute renal insufficiency (serum creatinine >200µM), dialysis, pulmonary
oedema, requirement ≥50% FiO$_2$ >1hr; intubation (other than for Caesarean section); and transfusion of any blood product. These components were developed by iterative Delphi consensus (23;24). A single case of Bell’s palsy was included as the onset and resolution of the palsy were temporally related to the clinical course of the pre-eclampsia.

We also assessed the incidence of an adverse perinatal outcome within the cohort. This outcome is defined as one or more of: perinatal or infant mortality, bronchopulmonary dysplasia (requirement for supplemental O$_2$ at 36 weeks' corrected gestational age, necrotising enterocolitis (confirmed at surgery/autopsy or pneumatosis intestinalis) (25), Grade III or IV intraventricular haemorrhage (intraventricular blood and ventricular dilatation, or intraparenchymal haemorrhage, respectively, by the most severe grade on head ultrasound done at <day 28 of life) (26), cystic periventricular leukomalacia (periventricular cysts by head ultrasound) (26), and Stage 3 -5 retinopathy of prematurity (in most affected eye: Stage 3 is extraretinal fibrovascular tissue; Stage 4 is partial retinal detachment; and Stage 5 is total retinal detachment) (27).

More details of methodologies utilized for the PIERS program of research as a whole are provided in Appendix A.

### 4.1.1 Data sources

Customised case report forms (attached in Appendix B) and a Microsoft Access™ database were created for data entry and utilised by all participating sites. Data were collected from the patient medical record(s). The candidate predictor variables were collected within 48 hours of eligibility. If absent, the ‘last observation carried forward’ method was used by which any preceding observation performed within two weeks of
admission was considered current unless replaced by a more recent value. This is consistent with clinical practice as clinicians do not re-evaluate what they believe has not changed, and is conservative in underestimating the effect of any given variable in modelling. For example, 24h urine proteinuria of 0.6g/d measured 4d prior to delivery would be considered the degree of proteinuria on the day of delivery for the purpose of the analyses.

4.1.2 Bias and missing data

Lead-time bias: We selected either the date and time of admission with pre-eclampsia or the post-admission development of pre-eclampsia (which ever was later) to standardise for both the level of clinical concern justifying admission and the concurrent presence of pre-eclampsia.

Incompetence bias (missing values and misclassification): We undertook abstractor training, developed and validated the Access database, performed both feasibility and development studies using that database, and performed random re-abstraction of charts to provide safeguards. Misclassification errors were minimised by database surveillance and re-abstraction. Re-abstraction occurred both randomly in 64 (5%) cases, and, also, for all cases where adverse maternal or perinatal outcomes were suspected or confirmed. Where there was uncertainty (13 [1.0%] cases), we resolved that uncertainty by iterative discussion between PvD, LAM, JM, and the relevant site investigator. We monitored and evaluated the fitted models to examine any influence that misclassification may have had on the final models.
As stated, we used last observation carried forward to fill in missing data where data were available within 12h (symptoms and signs) or 14d (laboratory tests) of eligibility. One highly informative variable, SaO₂, was prone to missing data early in the study while many of the participating centres introduced pulse oximetry into regular surveillance. In cases with missing pulse oximetry data, results were assigned the value, 97%, to lie within the normal range (95-100%) (28). We maintained three real values for each one imputed (29). This approach assumed non-use of oximetry was associated with better clinical state, and biased any analyses to underestimate the impact of a falling SaO₂ to identify increasing maternal risk (28).

The fitted models and their capacities for prediction were evaluated and compared with the models developed solely on complete data.

4.1.3 Study size

Only those candidate predictor variables available for at least 80% of the women were included. In response to a falling incidence of adverse outcomes observed in all centres, and previously reported in a single site study (16), an early decision was made to assess the model iteratively during the progress of the study once 200 women were entered into the database, and monthly thereafter, so that non-informative variables (p>0.2) could be abandoned. The decision to stop recruitment was deferred to YMacN, as the study statistician, once the following study size criteria had been met:

\[ N = \frac{n \times 10}{I} = 1157 \text{ women} \ (14;30;31). \]

Where N is the sample size, n = number of informative, non-convergent variables to be considered in the model (11 for fullPIERS [initial estimate: 20 variables]), and I =
incidence of the combined adverse outcome (0.095 at any time after eligibility). In addition, we required that the fullPIERS and miniPIERS models were stable, in terms of included variables and area under the receiver-operator curve (AUC ROC (32;33); < ±0.05) results, over the six months preceding the decision to stop recruitment. Thereby, our initial sample size estimation of 2000 women was adjusted downwards to a final sample size of 1250 women, allowing for some loss of power due to missing data in individual cases.

4.1.4 Quantitative variables

All quantitative variables were used as continuous variables. The normal non-pregnancy ranges for all variables included in the modelling from all the hospital laboratories were assessed to ensure comparability of data. Dipstick proteinuria was analysed as both a continuous and categorical variable to determine which analytical approach would be more informative.

4.1.5 Statistical methods

In our primary analysis for each of fullPIERS and miniPIERS, we considered 73 independent variables collected over the first 48h to predict the combined adverse maternal outcome occurring within the first 48 hours after eligibility (Table 4.1). The ‘worst value’ (e.g., highest sBP or lowest platelet count) measured prior to outcome occurrence or completion of the 48h epoch, whichever was first, was used. This particular epoch was chosen because it would improve perinatal outcomes by giving time
for steroid administration remote from term and it would inform decisions about the place of delivery/in utero transfer from level 1 and 2 units.

Each of the independent variables was then assessed in a univariable logistic regression analysis to examine any potential relationship between each of the independent variables and the combined adverse maternal outcome variable. Considered for a multiple regression analysis were 27 candidate variables that were both significantly associated with the outcome variable (Z-test p-value <0.05) and available in >80% of cases, from which the PIERS models were explored. To identify potential co-linearity among the candidate variables, pair-wise correlation co-efficients were calculated for continuous and categorical variables, using the Pearson correlation and Chi-square ($\chi^2$) tests, respectively.

We based the choice of the variables to be considered in the multivariable analyses on frequency of testing, univariable associations, correlations, and clinical opinion. According to deviance, the AIC (Akaike's information criterion) and AUC from each of the fitted models, the best fitting model was used as the final model. AUC ROC was computed in which, over a range of possible cut-points that could define a ‘positive test,’ the relation between the true-positive and false-positive ratios was shown. An AUC ROC of >0.7 is considered the minimum to indicate an adequately discriminative test; 1.0 indicates perfect discrimination and 0.5 is non-discriminative (i.e. no better than flipping a coin). The sensitivity, specificity, false positive probability, and false negative probability were calculated based on different cut-points. The Hosmer-Lemeshow test (HLT) was used to determine goodness of fit for the models, derived by SPSS 16.0.
(SPSS, Chicago, IL). All other statistical analyses were performed using free statistical software, R (www.r-project.org).

Leave-one-out cross validation was carried out to examine the performance of the final logistic regression models. In such an analysis, a single observation from the original sample was treated as the validation data and the remaining observations as the training data. The training data were used to fit a multiple regression model and the validation data were used for prediction. This process was repeated such that each observation in the dataset was used once as the validation data. The AUCs based on the final fitting (fitted probabilities) and cross validation (cross validation predictive probabilities) were calculated and compared.

We also assessed the performance of the fullPIERS and miniPIERS models every 24h from 48h up to one week post-eligibility to determine the duration of model performance. We repeated these assessments using data from the first 24h post-eligibility, the interim fullPIERS and miniPIERS models.

**4.2 RESULTS**

From 1 September 2003 - 31 August 2007, completed data from 1259 women (1382 fetuses) were entered into the PIERS database from seven international sites. Table 4.2 presents the baseline characteristics and pregnancy outcomes of these 1259 women. There were 119 (9.5%) combined adverse maternal and 70 (5.6%) combined adverse perinatal outcomes. Compared with the women who did not develop adverse outcomes, the women who developed adverse outcomes were of lower gestational age at eligibility (34), less likely to be parous, to smoke during the pregnancy, to be eligible on the basis
of hyperuricaemia, but more likely to develop HELLP syndrome, and to receive both antihypertensives and/or antenatal corticosteroids (for both fetal pulmonary- and HELLP-related indications). Maternal blood pressure indices, dipstick proteinuria, and AST were higher in women who developed adverse outcomes, while platelet counts were lower. The eligibility-to-delivery interval did not vary between groups, unless considering women eligible at <34wk. Under those circumstances, women who developed outcomes had briefer eligibility-to-delivery intervals. While women who developed adverse outcomes more frequently received MgSO₄ during their clinical course, only 59% did so. Women who developed adverse outcomes delivered babies earlier and of lower birth weight, but perinatal and infant mortality did not differ between groups.

Table 4.3 presents the incidence of the adverse maternal outcomes in the PIERS cohort by time from eligibility. Overall, 119 (9.5%) of women experienced maternal morbidity at any time, at a median of 4d from eligibility. These adverse outcomes occurred antenatally in 76 (6.0%) of women and postnatally in 43 (3.4%). The most common outcomes reached were: pulmonary oedema (53 (4.2%)) or transfusion of any blood product (51 (4.1%)).

Table 4.4 presents the results of the univariable analysis from 29 variables with p<0.1 and collected in >80% of cases. 24h urine protein estimation was not included as it was collected in 42% of all cases (47% of cases in the six centres where 24h urines were performed, one centre having moved completely to protein:creatinine ratios). Historically important variables excluded due to either low frequency and/or poor explanatory power included maternal age, multiple pregnancy, body mass index, past history of thromboembolic or renal disease, diabetes, 24h urinary protein estimation, and urinary
protein:creatinine ratio (a full list of the variables tested, and their univariable relationship with the combined adverse outcome, is available from the study website: www.piers.cfri.ca).

Those predictive variables that behaved most similarly in predicting the adverse maternal outcome were identified using cluster analysis (Figure 4.1). For example, AST, ALT, and LDH were very highly correlated, as were all three measures of blood pressure, diastolic, systolic and mean arterial pressure. Based on the correlation study and clinical opinions, only a subset of 11 potential variables was considered in the multiple regression analysis. All combinations of the 11 variables were explored in the multiple logistic regression analysis.

Figures 4.2a and b describe the characteristics of the fullPIERS models, developed with data from the first 48h and 24h after eligibility, respectively, to predict adverse maternal outcomes within 48h of eligibility. Both the 48h and 24h fullPIERS models attain performance characteristics deemed necessary for adequate outcome prediction. For the fullPIERS model developed with data from the first 48h after eligibility, the final equation is: \( \logit(p_i) = \ln \left( \frac{p_i}{1 - p_i} \right) = 26.608 + 2.042 \text{ (chest pain/dyspnoea)} - 0.334 \text{ (SaO}_2\text{)} + 0.335 \text{ (dipstick proteinuria)} + 0.023 \text{ (creatinine)} - 0.008 \text{ (platelet count)} + 0.063 \text{ (bilirubin).} \)

Figures 4.3a and b describe the characteristics of the miniPIERS models, developed with data from the first 48h and 24h after eligibility, respectively, to predict adverse maternal outcomes within 48h of eligibility. Systolic blood pressure and diastolic blood pressure were interchangeable in the model, systolic blood pressure was chosen as it can be assessed without a stethoscope. Both the 48h and 24h miniPIERS models attain
performance characteristics deemed necessary for adequate outcome prediction. For the miniPIERS model developed with data from the first 48h after eligibility, the final equation is:

\[
\text{logit}(p_i) = \ln \left( \frac{p_i}{1 - p_i} \right) = -8.664 + 2.174 (\text{chest pain/dyspnoea}) + 0.023 (\text{systolic BP}) + 0.425 (\text{dipstick proteinuria}).
\]

The fullPIERS (AUC ROC 0.655 [95% CI 0.581, 0.729]) and miniPIERS (AUC ROC 0.676 [95% CI 0.605, 0.746]) models poorly predict the combined adverse perinatal outcome.

Figures 4.4a - d describe the results of the cross validation exercise and the performance of the models at daily intervals from 2 to 7 days following eligibility. The point estimates of the cross validation AUCs approximate those of the model development set. Both fullPIERS models and miniPIERS models maintain performance for 7 days (i.e., AUC ROC >0.7); the miniPIERS model using data from first 24h has AUCs >0.7 at 48h, and approximately 0.7 for outcomes arising between 3-7d after eligibility.

4.3 DISCUSSION

4.3.1 Key results

To our knowledge, this is the first prospective, international study that has developed, and initially validated, an outcome prediction model for women admitted to tertiary units with pre-eclampsia. We have developed two versions, fullPIERS and miniPIERS, to make our findings more generalisable.

Among women admitted to hospital with pre-eclampsia, the 48h fullPIERS model predicts the likelihood of adverse maternal outcome occurring within the first 48h
following eligibility (i.e., being admitted and fulfilling the study definition of pre-eclampsia). The fullPIERS model includes the following predictors: chest pain/dyspnoea, \( \text{SaO}_2 \), dipstick proteinuria, platelet count, serum creatinine, and bilirubin, with an AUC ROC 0.91. The modelling identified clinical variables that have not been included traditionally in lists of adverse features: primarily \( \text{SaO}_2 \) and bilirubin. fullPIERS should assist decisions around delivery, especially at gestational ages remote from term when expectant management has such important impacts on perinatal outcomes (7;8). With data collected for the same variables over the first 24h following eligibility, which we believe could be used as an interim construct to inform decision making before the final 48h model is derived, the fullPIERS model performs well (AUC ROC 0.87).

The abbreviated miniPIERS model, consisting of chest pain/dyspnoea, systolic blood pressure, and dipstick proteinuria, also predicts the combined adverse maternal outcome within 48h (AUC ROC 0.82), but less effectively than the fullPIERS model. However, miniPIERS has enough accuracy to influence positively the burden of adverse outcome attributable to the HDP in rural and remote Canada and in low and middle income countries. These are settings where access to laboratory investigations can be difficult. Systolic blood pressure was interchangeable with diastolic, but was selected as it can be assessed without a stethoscope by palpation of the radial pulse.

### 4.3.2 Limitations

There are five main limitations to this study.

First is the concern around missing data. For the ‘gold standard’ of 24h urine protein estimation, this meant that 24h urine protein could not be included in the
modelling. This is despite the estimation of 24h urinary protein being local policy in all but one of the centres (one centre had transferred across to the spot urinary protein:creatinine ratio prior to participation). Therefore, while not included in the modelling, the absence of the 24h urine protein estimation reflects both real world care and uncertainty about its place as a gold standard (35).

Second, the models have been derived and cross-validated using a single data set. Third, for miniPIERS, in particular, the study was performed solely in high income country tertiary obstetric units, and, fourth, solely in women who fulfilled a research definition of pre-eclampsia. The fifth limitation is that imposed by a relatively small sample size, especially when considering the low rate of adverse maternal outcomes.

These last four limitations will be addressed by further validation studies in new populations of women in high and low risk obstetric units, in high, middle, and low income country settings, and across the full breadth of the hypertensive disorders of pregnancy, with support from the CIHR and the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

4.3.3 Interpretation

The fullPIERS model maintained good performance (AUC ROC >0.8), beyond 3d post-eligibility, and maintained reasonable performance (AUC ROC >0.7) up to 7d post-eligibility. Therefore, we were able to accurately predict adverse maternal outcomes for up to 48h, a clinically useful epoch that permits steroid administration, transfer, or
induction. However, like Ganzevoort et al (15), we were unable to predict adverse maternal outcomes at any time following admission to hospital with pre-eclampsia. This finding was anticipated, as it is the deterioration of a previously stable maternal and/or fetal status that modifies clinical management, especially remote from term. Even though many factors are predictive of the onset of pre-eclampsia (36), they failed to identify women at increased risk of the complications of pre-eclampsia once the disease had developed. Such variables included maternal age, past obstetric history, past medical history, and hyperuricaemia.

In the PIERS cohort, gestational age at onset for pre-eclampsia was significantly lower in those women destined to develop complications. This is consistent with previous studies that have observed that early-onset disease (onset <32 weeks) is associated with a 20-fold increase in maternal mortality risk (37), and increased risks for maternal morbidity (38). However, once variables more closely correlated with the development of significant adverse maternal outcomes were included in the modelling, gestational age at onset did not independently predict adverse maternal outcomes. It would appear that once a woman enters the final common pathway to severe disease, the prediction of progression to adverse maternal outcomes by the PIERS models is possible and occurs at any gestation. Lower gestational age at eligibility increases the risk to enter that path.

Many traditional clinical variables of importance were not included in the final model either because they were collected in <80% of cases (e.g., 24h urine) or because they were displaced within the multivariable modelling (e.g., BP (in fullPIERS), uric acid, AST, ALT, and LDH) by variables with greater independent explanatory power. That traditional ‘severity’ criteria may not be predictive of adverse maternal outcomes
was anticipated by an analysis of data from the first 737 women in the PIERS database (39). This analysis confirmed that many of these historical criteria of severity were not predictive of adverse maternal outcomes (39).

For face validity, we did examine whether or not either blood pressure or AST could be forced into the fullPIERS model. Neither variable was independently able to predict adverse maternal outcomes. In the case of blood pressure, we suggest that it did not perform in the multivariable fullPIERS model as it is the sole element of the maternal syndrome amenable to intervention. Effective antihypertensive agents exist for both mild-to-moderate and severe pregnancy hypertension (40). During the first 48h after eligibility, women who went on to develop adverse outcomes had BP indices 4-10mmHg higher than those women with uncomplicated courses.

AST, ALT, and LDH did vary between women who did and those who did not develop the adverse outcomes, but the differences (4U/L for AST) were not of clinical significance. These tests were displaced from the model by bilirubin. The rise in bilirubin, often still within the normal range, appears to be a better clinical screen for maternal risk, probably because it is a better non-specific summary measure of haemolysis and liver dysfunction than are elevations in hepatocellular enzymes.

We are certainly not advocating that neither blood pressure nor AST be measured in women with suspected or confirmed pre-eclampsia. However, the results of the cluster analysis would suggest that only one of AST or ALT need to be measured, and that the measurement of LDH is redundant in these women. Other tests that could reasonably be abandoned in light of these data are urea and routine coagulation studies (in the absence of either thrombocytoopenia or abnormal bleeding).
Why were 24h hour collections performed in fewer than 50% of these women? Pragmatically, we believe that clinicians faced with a hypertensive woman with 2+ proteinuria on dipstick analysis at term will decide to advise delivery rather than accept the delay inherent in a 24h collection. We have supported that pattern of care (13). Given concerns raised about the accuracy of 24h urine collections for the estimation of proteinuria in pregnancy (35), the spot urinary protein:creatinine ratio should probably replace 24h collection for the diagnosis of proteinuria (41). Until the protein:creatinine ratio can be performed sufficiently frequently to evaluate its performance in predictive modelling, we suggest that dipstick proteinuria, despite its inherent flaws (42), be used to stratify maternal risks.

The low rate of MgSO₄ administration to the women who developed adverse outcomes (59%) in these seven academic tertiary obstetric units was surprising. This group of women all developed significant personal complications of the pre-eclampsia syndrome. While the results of the randomised controlled trials of MgSO₄ as eclampsia prophylaxis are compelling (43), we believe that there remains uncertainty about when, and with whom, to start MgSO₄ (13).

4.3.4 Generalisability

How do we suggest that these data be used to direct care during the re-validation phase of this project and before a practical scoring system can be published?

First, the univariable analyses may aid decision-making prior to the validation and publication of the PIERS models. By assessing changes in values of continuous variables and the presence or absence of dichotomous variables, particularly symptoms (chest
pain/dyspnoea), we believe that clinicians may be able to build a fuller sense of disease evolution in their own minds. We consider that this is what underlay the reduction in the incidence of adverse maternal outcomes associated with the introduction of the PIERS study assessment and surveillance guidelines into one of the study sites (16).

Second, we support using pulse oximetry, dipstick proteinuria, and serum bilirubin during the initial assessment and ongoing surveillance of women admitted with pre-eclampsia. This study has found that these variables are valuable even though they have not been supported in the evaluation of women with pre-eclampsia and, in the case of dipstick proteinuria, have been largely discounted (21).

Third, it appears reasonable to abandon multiple tests that are redundant when performed together. For example, the testing of AST, ALT, and LDH might be replaced by, say, AST alone, without losing important information and with cost savings at the laboratory level.

Fourth, it appears safe to reserve more expensive tests (e.g., coagulation studies) until other indices of risk indicate their use. The standard of using a falling platelet count to precipitate coagulation studies would appear to be appropriate (10).

Fifth, although reasonable assessments of risk can be made during the first 24h after the diagnosis of pre-eclampsia has been made, incorporating further data over the following 24h appear to improve the accuracy of such risk assessments.

By grouping women according to the risk of adverse maternal outcomes that make pre-eclampsia so important, the PIERS models should also contribute to our understanding of the pathophysiology of the disease. This should enhance the
development of new treatments and interventions designed to reduce maternal and perinatal morbidity and mortality.

The most important impact of these models may be to identify those women at lowest risk of adverse outcomes, so that they can be offered expectant management either remote from term for perinatal benefit (7;8) or at or near term to allow time for induction of labour in a considered fashion (13).
### 4.4 Tables and Figures

**Table 4.1: Variables considered in the PIERS modelling**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Demographics</th>
<th>Past obstetric history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at EDD (yr)</td>
<td></td>
<td>Gestational hypertension (y/n)</td>
</tr>
<tr>
<td>Number of fetuses</td>
<td></td>
<td>Gestational proteinuria (y/n)</td>
</tr>
<tr>
<td>Gestational age at onset (wk)</td>
<td></td>
<td>Pre-eclampsia (y/n)</td>
</tr>
<tr>
<td>Gestational age at delivery (wk)</td>
<td></td>
<td>GDM (prior preg) (y/n)</td>
</tr>
<tr>
<td>Weight - pre-pregnancy (kg)</td>
<td></td>
<td>GDM (this preg) (y/n)</td>
</tr>
<tr>
<td>Weight – on admission (kg)</td>
<td></td>
<td>Past medical history</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td>Thromboembolic disease (y/n)</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td></td>
<td>Cardiovascular disease (y/n)</td>
</tr>
<tr>
<td>Gravidity (n)</td>
<td></td>
<td>Hypertension (y/n)</td>
</tr>
<tr>
<td>Parity (n)</td>
<td></td>
<td>Renal disease (y/n)</td>
</tr>
<tr>
<td>Married (y/n)</td>
<td></td>
<td>Diabetes mellitus (y/n)</td>
</tr>
<tr>
<td>New partner (y/n)</td>
<td></td>
<td>Family history</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td>Pre-eclampsia (y/n)</td>
</tr>
<tr>
<td>Smoking in this pregnancy (y/n)</td>
<td></td>
<td>Thromboembolic disease (y/n)</td>
</tr>
<tr>
<td>Illicit drug use in this pregnancy (y/n)</td>
<td></td>
<td>Cardiovascular disease (y/n)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td>Hypertension (y/n)</td>
</tr>
<tr>
<td>Severe nausea and vomiting (y/n)</td>
<td></td>
<td>Diabetes mellitus (y/n)</td>
</tr>
<tr>
<td>Frontal headache (y/n)</td>
<td></td>
<td>Cardiorespiratory signs</td>
</tr>
<tr>
<td>Visual disturbance (y/n)</td>
<td></td>
<td>Booking sBP (mmHg)</td>
</tr>
<tr>
<td>RUQ/epigastric pain (y/n)</td>
<td></td>
<td>Booking dBP (mmHg)</td>
</tr>
<tr>
<td>Chest pain/dyspnoea (y/n)</td>
<td></td>
<td>Booking MAP (mmHg)</td>
</tr>
<tr>
<td>≥1 symptom (y/n)</td>
<td></td>
<td>dBP on eligibility (mmHg)</td>
</tr>
<tr>
<td>Haematological tests</td>
<td></td>
<td>sBP on eligibility (mmHg)</td>
</tr>
<tr>
<td>Total leukocyte count (x10$^9$/L)</td>
<td></td>
<td>MAP on eligibility (mmHg)</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td></td>
<td>SaO$_2$ (%) / SaO$_2$ (filled) * (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal signs and tests</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipstick (categorical) $\dagger$</td>
<td></td>
</tr>
<tr>
<td>Dipstick (continuous) $\ddagger$</td>
<td></td>
</tr>
<tr>
<td>24h urine protein (g/d)</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Indicator</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>MPV/plt ratio</td>
<td>Pr:Cr ratio (mg/mM)</td>
</tr>
<tr>
<td>INR</td>
<td>Fluid input (ml/h)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>Urine output (ml/h)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>Fluid balance (ml)</td>
</tr>
<tr>
<td></td>
<td>Creatinine (µM)</td>
</tr>
<tr>
<td></td>
<td>Urea (mM)</td>
</tr>
<tr>
<td></td>
<td>Uric acid (µM)</td>
</tr>
<tr>
<td><strong>Hepatic tests</strong></td>
<td><strong>Fetal assessment tests</strong></td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>AFI (DAP) (mm)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>EFW (%ile category)</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>AC (%ile category)</td>
</tr>
<tr>
<td>Bilirubin (µM)</td>
<td>UA EDF (present, absent, reversed)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>BPP (score /8)</td>
</tr>
<tr>
<td>Random glucose (mM)</td>
<td>FHR (normal/suspicious/pathological) **</td>
</tr>
</tbody>
</table>

*missing data filled assuming 97% (described in the Methods); † classified as 0, trace, 1+, 2+, 3+, 4+; ‡ classified as 0, 0.5, 1, 2, 3, 4; ‡ classified as <1.0%, 1.0-2.4%, 2.5-4.9%, 5.0-9.9%, 10.0-49.9%, 50.0-89.9%, 90.0-94.9%, 95.0-97.4%, 97.5-98.9%, ≥99.0% (44, 45); ** using Royal College of Obstetricians and Gynaecologists definitions (46).

AC abdominal circumference; AFI amniotic fluid index; ALT alanine transaminase; APTT activated partial thromboplastin time; AST aspartate transaminase; BPP biophysical profile; DAP deepest amniotic fluid pocket; dBP diastolic blood pressure; EDD expected date of delivery; EFW estimated fetal weight (Hadlock); FHR fetal heart rate; GDM gestational diabetes mellitus; INR international normalised ratio; LDH lactate dehydrogenase; MAP mean arterial pressure; MPV mean platelet volume; preg pregnancy; RUQ right upper quadrant; SaO2 oxygen saturation (pulse oximetry); sBP systolic blood pressure; UA EDF umbilical artery Doppler end diastolic flow.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adverse outcomes (N=119 women) (N=144 fetuses)</th>
<th>Normal outcomes (N=1140 women) (N=1238 fetuses)</th>
<th>p (Fisher’s exact, χ², or Mann-Whitney U)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics (within 48h of eligibility)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age at EDD (years)</td>
<td>31.5 [26.0, 35.0]</td>
<td>32.0 [27.0, 36.0]</td>
<td>0.7646</td>
</tr>
<tr>
<td>Gestational age at eligibility (weeks)</td>
<td>33.4 [30.2, 36.5]</td>
<td>36.6 [33.7, 38.4]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gestational age at eligibility &lt;34⁰ weeks</td>
<td>64 (53.3%)</td>
<td>293 (27.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>22 (18.3%)</td>
<td>94 (8.7%)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Parity ≥ 1</td>
<td>26 (21.7%)</td>
<td>302 (30.0%)</td>
<td>0.2753</td>
</tr>
<tr>
<td>Smoking in this pregnancy</td>
<td>8 (5.0%)</td>
<td>139 (12.9%)</td>
<td>0.0739</td>
</tr>
<tr>
<td>Pre-eclampsia description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension and proteinuria</td>
<td>82 (68.3%)</td>
<td>717 (66.5%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension and hyperuricaemia</td>
<td>11 (9.2%)</td>
<td>158 (14.6%)</td>
<td></td>
</tr>
<tr>
<td>HELLP without hypertension or proteinuria</td>
<td>10 (8.3%)</td>
<td>31 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Superimposed pre-eclampsia</td>
<td>17 (14.2%)</td>
<td>169 (15.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical (within 48h of eligibility)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>123.8 [116.7, 133.3]</td>
<td>120.0 [114.0, 128.3]</td>
<td>0.0061</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>169.5 [155.8, 180.0]</td>
<td>160.0 [150.0, 173.0]</td>
<td>0.0010</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>105.0 [100.0, 112.0]</td>
<td>101.0 [98.0, 110.0]</td>
<td>0.0412</td>
</tr>
<tr>
<td>Worst dipstick proteinuria</td>
<td>3+ [1+, 4+]</td>
<td>2+ [1+, 3+]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lowest platelets</td>
<td>172.5 [141.5, 226.0]</td>
<td>191.0 [147.3, 239.0]</td>
<td>0.0024</td>
</tr>
<tr>
<td>Highest aspartate transaminase</td>
<td>32.0 [22.0, 47.0]</td>
<td>28.0 [22.0, 41.0]</td>
<td>0.0062</td>
</tr>
<tr>
<td>Antihypertensive treatment administered (at the time of or within 48h of eligibility)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility-to-delivery interval (all cases) (d)</td>
<td>3.0 [1.0, 6.0]</td>
<td>1.0 [1.0, 4.0]</td>
<td>0.2366</td>
</tr>
</tbody>
</table>

Interventions

Corticosteroid administration

Fetal lung maturation

45 (37.5%)                                    | 230 (20.2%)                                  | <0.0001                                  |

Treatment of HELLP syndrome

10 (8.3%)                                     | 17 (1.5%)                                    | <0.0001                                  |

New antihypertensive medications begun

39 (32.5%)                                    | 243 (21.3%)                                  | 0.0078                                   |

MgSO₄ administered

71 (59.2%)                                    | 345 (30.3%)                                  | <0.0001                                  |

Pregnancy outcomes

Eligibility-to-delivery interval (all cases) (d) | 3.0 [1.0, 6.0]                                | 1.0 [1.0, 4.0]                           | 0.2366 |
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adverse outcomes (N=119 women) (N=144 fetuses)</th>
<th>Normal outcomes (N=1140 women) (N=1238 fetuses)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility-to-delivery interval (&lt;34⁺⁰⁴ wks) (d)</td>
<td>4.0 [2.0, 8.5]</td>
<td>5.0 [2.0, 16.0]</td>
<td>0.0309</td>
</tr>
<tr>
<td>Gestational age at delivery (wk)</td>
<td>34.4 [30.7, 37.1]</td>
<td>37.0 [34.3, 38.7]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1795 [1208, 2830]</td>
<td>2640 [1835, 3290]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth weight &lt;3rd percentile (N babies) (45)</td>
<td>12 (8.1%)</td>
<td>82 (7.0%)</td>
<td>0.4838</td>
</tr>
<tr>
<td>Intrauterine fetal death (≥20⁻⁰⁰ wk and/or ≥500g)</td>
<td>0 (0%)</td>
<td>13 (1.1%)</td>
<td>0.3828</td>
</tr>
<tr>
<td>Neonatal death (before 28d)</td>
<td>1 (0.8%)</td>
<td>10 (0.9%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Infant death prior to hospital discharge or 6wk</td>
<td>2 (1.7%)</td>
<td>14 (1.2%)</td>
<td>0.7002</td>
</tr>
</tbody>
</table>

Data are expressed as median [interquartile range] or n (%)

(45) reference 45; dBP diastolic blood pressure; EDD expected date of delivery; HELLP haemolysis, elevated liver enzymes, low platelets; sBP systolic blood pressure
Table 4.3: Adverse outcomes

<table>
<thead>
<tr>
<th>One or more of maternal morbidity or mortality:</th>
<th>within 48h [41 (3.3%)]</th>
<th>within 7d [90 (7.1%)]</th>
<th>any time [119 (9.5%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eclampsia (≥1)</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Glasgow coma score &lt;13</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Stroke or RIND</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cortical blindness or retinal detachment</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cardiorespiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive inotropic support</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Infusion of a 3rd parenteral antihypertensive</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial ischaemia/infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥50% FiO₂ for &gt;1h</td>
<td>5</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Intubation</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>18</td>
<td>42</td>
<td>53</td>
</tr>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion of any blood product</td>
<td>15</td>
<td>36</td>
<td>51</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysfunction</td>
<td>6</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Haematoma/rupture</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute renal insufficiency</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

RIND reversible ischaemic neurological deficit
Table 4.4: Univariable analyses of candidate predictor variables with p<0.1 and collected in >80% of cases (n=29)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>β-coef</th>
<th>p</th>
<th>AUC ROC [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery (d)</td>
<td>1258 (99.9)</td>
<td>-0.086</td>
<td>0.024</td>
<td>0.599 [0.503, 0.694]</td>
</tr>
<tr>
<td>Weight at eligibility (kg)</td>
<td>1123 (89.2)</td>
<td>-0.019</td>
<td>0.079</td>
<td>0.587 [0.480, 0.694]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1094 (86.9)</td>
<td>-0.039</td>
<td>0.073</td>
<td>0.592 [0.503, 0.680]</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe nausea and vomiting (y/n)</td>
<td>1259 (100)</td>
<td>1.232</td>
<td>0.004</td>
<td>0.557 [0.461, 0.653]</td>
</tr>
<tr>
<td>RUQ/epigastric pain (y/n)</td>
<td>1259 (100)</td>
<td>1.099</td>
<td>0.001</td>
<td>0.607 [0.511, 0.703]</td>
</tr>
<tr>
<td>Chest pain/dyspnoea (y/n)</td>
<td>1259 (100)</td>
<td>2.615</td>
<td>&lt;0.001</td>
<td>0.642 [0.540, 0.744]</td>
</tr>
<tr>
<td>≥1 symptom (y/n)</td>
<td>1259 (100)</td>
<td>1.463</td>
<td>&lt;0.001</td>
<td>0.658 [0.582, 0.735]</td>
</tr>
<tr>
<td><strong>Cardiovascular signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dBP on eligibility (mmHg)</td>
<td>1259 (100)</td>
<td>0.045</td>
<td>0.001</td>
<td>0.664 [0.579, 0.748]</td>
</tr>
<tr>
<td>sBP on eligibility (mmHg)</td>
<td>1259 (100)</td>
<td>0.035</td>
<td>&lt;0.001</td>
<td>0.690 [0.606, 0.775]</td>
</tr>
<tr>
<td>MAP on eligibility (mmHg)</td>
<td>1259 (100)</td>
<td>0.046</td>
<td>&lt;0.001</td>
<td>0.688 [0.606, 0.770]</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>925 (73.5)</td>
<td>-0.540</td>
<td>&lt;0.001</td>
<td>0.838 [0.771, 0.904]</td>
</tr>
<tr>
<td>SaO₂ (filled) (%)*</td>
<td>1259 (100)</td>
<td>-0.585</td>
<td>&lt;0.001</td>
<td>0.843 [0.776, 0.909]</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipstick (categorical)†</td>
<td>1233 (97.9)</td>
<td>0.755</td>
<td></td>
<td>0.688 [0.682]</td>
</tr>
<tr>
<td>Dipstick (continuous)‡</td>
<td>1233 (97.9)</td>
<td>0.611</td>
<td>&lt;0.001</td>
<td>0.699 [0.610, 0.788]</td>
</tr>
<tr>
<td>Creatinine (µM)</td>
<td>1250 (99.3)</td>
<td>0.027</td>
<td>&lt;0.001</td>
<td>0.666 [0.571, 0.761]</td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>1187 (94.3)</td>
<td>0.362</td>
<td>&lt;0.001</td>
<td>0.664 [0.572, 0.755]</td>
</tr>
<tr>
<td>Uric acid (µM)</td>
<td>1251 (99.4)</td>
<td>0.008</td>
<td>&lt;0.001</td>
<td>0.646 [0.552, 0.741]</td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total leukocyte count (x 10⁹/L)</td>
<td>1257 (99.8)</td>
<td>0.089</td>
<td>0.004</td>
<td>0.635 [0.550,0.721]</td>
</tr>
<tr>
<td>Platelet count (X 10⁹/L)</td>
<td>1255 (99.7)</td>
<td>-0.014</td>
<td>&lt;0.001</td>
<td>0.699 [0.609, 0.788]</td>
</tr>
<tr>
<td>Mean platelet volume (fL)</td>
<td>1251 (99.4)</td>
<td>0.192</td>
<td>0.038</td>
<td>0.566 [0.481, 0.651]</td>
</tr>
<tr>
<td>MPV/platelet count ratio</td>
<td>1251 (99.4)</td>
<td>13.773</td>
<td>&lt;0.001</td>
<td>0.680 [0.586, 0.774]</td>
</tr>
<tr>
<td>International normalised ratio (INR)</td>
<td>1133 (90.0)</td>
<td>12.615</td>
<td>&lt;0.001</td>
<td>0.717 [0.627, 0.807]</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (sec)</td>
<td>1134 (90.1)</td>
<td>0.041</td>
<td>0.001</td>
<td>0.684 [0.592, 0.776]</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>1035 (82.2)</td>
<td>-0.275</td>
<td>0.049</td>
<td>0.626 [0.516, 0.736]</td>
</tr>
<tr>
<td>Variable</td>
<td>N (%)</td>
<td>β-coeff</td>
<td>p</td>
<td>AUC ROC [95% CI]</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
<td>---------</td>
<td>--------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate transaminase (U/L)</td>
<td>1211 (96.2)</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.718 [0.635, 0.800]</td>
</tr>
<tr>
<td>Alanine transaminase (U/L)</td>
<td>1254 (99.6)</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.658 [0.557, 0.760]</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>1198 (95.2)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.621 [0.524, 0.718]</td>
</tr>
<tr>
<td>Bilirubin (µM)</td>
<td>1187 (94.3)</td>
<td>0.140</td>
<td>&lt;0.001</td>
<td>0.718 [0.627, 0.808]</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>1070 (85.0)</td>
<td>-0.139</td>
<td>&lt;0.001</td>
<td>0.695 [0.598, 0.791]</td>
</tr>
</tbody>
</table>

* missing data filled assuming 97% (described in the Methods); † classified as 0, trace, 1+, 2+, 3+, 4+; ‡ classified as 0, 0.5, 1, 2, 3, 4.

dBP diastolic blood pressure; MAP mean arterial pressure; MPV mean platelet volume; RUQ right upper quadrant; SaO2 oxygen saturation (pulse oximetry); sBP systolic blood pressure
Figure 4.1a: Cluster analyses of continuous variables significantly associated with the combined adverse maternal outcome by univariable analysis.

ALT alanine transaminase; aPTT activated partial thromboplastin time; AST aspartate transaminase; dBP diastolic blood pressure; GA gestational age; INR international normalised ratio; LDH lactate dehydrogenase; MAP mean arterial pressure; MPV mean platelet volume; sBP systolic blood pressure; WBC white blood cell count (total leukocyte count)
Figure 4.1b: Cluster analyses of dichotomous variables significantly associated with the combined adverse maternal outcome by univariable analysis.

- **chest_pain** chest pain/dyspnoea
- **FHRT_vis** visual interpretation of the fetal heart rate pattern (cardiotocography)
- **ruq_pain** right upper quadrant

`Figure 4.1b` includes a dendrogram showing the relationships between these variables.
Figure 4.2: Performance of the fullPIERS model developed with data from (a) first 48h after eligibility and (b) first 24h after eligibility.

Combined adverse maternal outcome predicted within 48h of eligibility using only data collected prior to the outcome.

AUC: area under receiver-operator curve; HLT: Hosmer Lemeshow test; NPV: negative predictive value; PPV: positive predictive value; sens: sensitivity; spec: specificity
Figure 4.3: Performance of the miniPIERS model developed with data from (a) first 48h after eligibility and (b) first 24h after eligibility.

Combined adverse maternal outcome predicted within 48h of eligibility using only data collected prior to the outcome.

AUC: area under receiver-operator curve; HLT: Hosmer Lemeshow test; NPV: negative predictive value; PPV: positive predictive value; sens: sensitivity; spec: specificity
Figure 4.4a – d: fullPIERS and miniPIERS areas under the receiver-operator curves (AUCs; error bars: 95% confidence intervals) from 2 – 7 days after PIERS study eligibility, including the fitted models and cross validation. 
(a) fullPIERS model using data from 1st 48h post-eligibility prior to occurrence of any adverse outcome, if relevant. (b) fullPIERS model using 1st 24h data. (c) miniPIERS model using 48h data. (d) miniPIERS model using 1st 24h data.
Table 4.5: Univariable analyses of all candidate predictor variables investigated (N=73)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>β-coef</th>
<th>p</th>
<th>AUC ROC [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at EDD (yr)</td>
<td>1259 (100)</td>
<td>-0.018</td>
<td>0.469</td>
<td>0.536 [0.449, 0.623]</td>
</tr>
<tr>
<td>Number of fetuses</td>
<td>1259 (100)</td>
<td></td>
<td></td>
<td>0.512 [0.423, 0.600]</td>
</tr>
<tr>
<td>Gestational age at onset (wk)</td>
<td>1259 (100)</td>
<td>-0.042</td>
<td>0.257</td>
<td>0.553 [0.458, 0.647]</td>
</tr>
<tr>
<td>Gestational age at delivery (wk)</td>
<td>1258 (99.9)</td>
<td>-0.086</td>
<td>0.024</td>
<td>0.599 [0.503, 0.694]</td>
</tr>
<tr>
<td>Weight - pre-pregnancy (kg)</td>
<td>1096 (87.1)</td>
<td>-0.010</td>
<td>0.335</td>
<td>0.568 [0.472, 0.664]</td>
</tr>
<tr>
<td>Weight – on admission (kg)</td>
<td>1123 (89.2)</td>
<td>-0.019</td>
<td>0.079</td>
<td>0.587 [0.480, 0.694]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1094 (86.9)</td>
<td>-0.039</td>
<td>0.073</td>
<td>0.592 [0.503, 0.680]</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1018 (80.9)</td>
<td>-0.002</td>
<td>0.956</td>
<td>0.522 [0.421, 0.623]</td>
</tr>
<tr>
<td>Gravidity (n)</td>
<td>1259 (100)</td>
<td></td>
<td></td>
<td>0.592 [0.510, 0.674]</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>1259 (100)</td>
<td></td>
<td></td>
<td>0.552 [0.468, 0.636]</td>
</tr>
<tr>
<td>Married (y/n)</td>
<td>1245 (98.9)</td>
<td>-0.564</td>
<td>0.214</td>
<td>0.529 [0.435, 0.623]</td>
</tr>
<tr>
<td>New partner (y/n)</td>
<td>894 (71.0)</td>
<td></td>
<td></td>
<td>0.590 [0.500, 0.680]</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>1065 (84.6)</td>
<td></td>
<td></td>
<td>0.597 [0.503, 0.691]</td>
</tr>
<tr>
<td>Smoking in this pregnancy (y/n)</td>
<td>1169 (92.9)</td>
<td>-1.079</td>
<td>0.140</td>
<td>0.543 [0.457, 0.629]</td>
</tr>
<tr>
<td>Illicit drug use in this pregnancy (y/n)</td>
<td>1180 (93.7)</td>
<td>-14.181</td>
<td>0.987</td>
<td>0.509 [0.417, 0.601]</td>
</tr>
<tr>
<td>Gestational hypertension (y/n)</td>
<td>351 (27.9)</td>
<td>-0.288</td>
<td>0.688</td>
<td>0.536 [0.332, 0.740]</td>
</tr>
<tr>
<td>Gestational proteinuria (y/n)</td>
<td>316 (25.1)</td>
<td>-0.868</td>
<td>0.431</td>
<td>0.578 [0.366, 0.790]</td>
</tr>
<tr>
<td>Pre-eclampsia (y/n)</td>
<td>351 (27.9)</td>
<td>-1.030</td>
<td>0.338</td>
<td>0.580 [0.400, 0.761]</td>
</tr>
<tr>
<td>GDM (prior preg) (y/n)</td>
<td>349 (27.7)</td>
<td>0.514</td>
<td>0.639</td>
<td>0.526 [0.303, 0.750]</td>
</tr>
<tr>
<td>GDM (this preg) (y/n)</td>
<td>1252 (99.4)</td>
<td>-0.332</td>
<td>0.585</td>
<td>0.513 [0.425, 0.601]</td>
</tr>
<tr>
<td>Thromboembolic disease (y/n)</td>
<td>1252 (99.4)</td>
<td>1.099</td>
<td>0.300</td>
<td>0.508 [0.416, 0.600]</td>
</tr>
<tr>
<td>Cardiovascular disease (y/n)</td>
<td>1253 (99.5)</td>
<td>0.691</td>
<td>0.509</td>
<td>0.506 [0.416, 0.596]</td>
</tr>
<tr>
<td>Hypertension (y/n)</td>
<td>1254 (99.6)</td>
<td>-0.328</td>
<td>0.498</td>
<td>0.520 [0.418, 0.622]</td>
</tr>
<tr>
<td>Renal disease (y/n)</td>
<td>1251 (99.4)</td>
<td>0.055</td>
<td>0.940</td>
<td>0.501 [0.411, 0.591]</td>
</tr>
<tr>
<td>Diabetes mellitus (y/n)</td>
<td>1254 (99.6)</td>
<td>-15.231</td>
<td>0.985</td>
<td>0.526 [0.439, 0.612]</td>
</tr>
<tr>
<td>Pre-eclampsia (y/n)</td>
<td>787 (62.5)</td>
<td>0.323</td>
<td>0.560</td>
<td>0.518 [0.404, 0.632]</td>
</tr>
<tr>
<td>Thromboembolic disease (y/n)</td>
<td>1188 (94.4)</td>
<td>-0.011</td>
<td>0.992</td>
<td>0.500 [0.410, 0.590]</td>
</tr>
<tr>
<td>Cardiovascular disease (y/n)</td>
<td>1193 (94.8)</td>
<td>0.289</td>
<td>0.455</td>
<td>0.523 [0.429, 0.617]</td>
</tr>
<tr>
<td>Hypertension (y/n)</td>
<td>1193 (94.8)</td>
<td>-0.108</td>
<td>0.744</td>
<td>0.513 [0.423, 0.603]</td>
</tr>
<tr>
<td>Variable</td>
<td>N (%)</td>
<td>β-coef</td>
<td>p</td>
<td>AUC ROC [95% CI]</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------</td>
<td>--------</td>
<td>-------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Diabetes mellitus (y/n)</td>
<td>1193 (94.8)</td>
<td>0.075</td>
<td>0.831</td>
<td>0.508 [0.416, 0.600]</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe nausea and vomiting (y/n)</td>
<td>1259 (100)</td>
<td>1.232</td>
<td>0.004</td>
<td>0.557 [0.461, 0.653]</td>
</tr>
<tr>
<td>Frontal headache (y/n)</td>
<td>1259 (100)</td>
<td>0.448</td>
<td>0.162</td>
<td>0.553 [0.461, 0.645]</td>
</tr>
<tr>
<td>Visual disturbance (y/n)</td>
<td>1259 (100)</td>
<td>0.152</td>
<td>0.692</td>
<td>0.512 [0.422, 0.603]</td>
</tr>
<tr>
<td>RUQ/epigastric pain (y/n)</td>
<td>1259 (100)</td>
<td>1.099</td>
<td>0.001</td>
<td>0.607 [0.511, 0.703]</td>
</tr>
<tr>
<td>Chest pain/dyspnoea (y/n)</td>
<td>1259 (100)</td>
<td>2.615</td>
<td>&lt;0.001</td>
<td>0.642 [0.540, 0.744]</td>
</tr>
<tr>
<td>≥1 symptom (y/n)</td>
<td>1259 (100)</td>
<td>1.463</td>
<td>&lt;0.001</td>
<td>0.658 [0.582, 0.735]</td>
</tr>
<tr>
<td><strong>Cardiovascular signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booking sBP (mmHg)</td>
<td>879 (69.8)</td>
<td>-0.001</td>
<td>0.943</td>
<td>0.489 [0.379, 0.600]</td>
</tr>
<tr>
<td>Booking dBP (mmHg)</td>
<td>879 (69.8)</td>
<td>0.014</td>
<td>0.459</td>
<td>0.513 [0.402, 0.624]</td>
</tr>
<tr>
<td>Booking MAP (mmHg)</td>
<td>879 (69.8)</td>
<td>0.008</td>
<td>0.660</td>
<td>0.516 [0.402, 0.631]</td>
</tr>
<tr>
<td>dBP on eligibility (mmHg)</td>
<td>1259 (100)</td>
<td>0.045</td>
<td>0.001</td>
<td>0.664 [0.579, 0.748]</td>
</tr>
<tr>
<td>sBP on eligibility (mmHg)</td>
<td>1259 (100)</td>
<td>0.035</td>
<td>&lt;0.001</td>
<td>0.690 [0.606, 0.775]</td>
</tr>
<tr>
<td>MAP on eligibility (mmHg)</td>
<td>1259 (100)</td>
<td>0.046</td>
<td>&lt;0.001</td>
<td>0.688 [0.606, 0.770]</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>925 (73.5)</td>
<td>-0.540</td>
<td>&lt;0.001</td>
<td>0.838 [0.771, 0.904]</td>
</tr>
<tr>
<td>SaO₂ (filled) * (%)</td>
<td>1259 (100)</td>
<td>-0.585</td>
<td>&lt;0.001</td>
<td>0.843 [0.776, 0.909]</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipstick (categorical)†</td>
<td>1233 (97.9)</td>
<td>0.755</td>
<td></td>
<td>0.688 [0.605, 0.782]</td>
</tr>
<tr>
<td>Dipstick (continuous)‡</td>
<td>1233 (97.9)</td>
<td>0.611</td>
<td>&lt;0.001</td>
<td>0.699 [0.610, 0.788]</td>
</tr>
<tr>
<td>24h urine protein (g/d)</td>
<td>529 (42.0)</td>
<td>0.132</td>
<td>&lt;0.001</td>
<td>0.744 [0.614, 0.873]</td>
</tr>
<tr>
<td>Pr:Cr ratio (mg/mmol)</td>
<td>823 (65.4)</td>
<td>0.001</td>
<td>0.037</td>
<td>0.672 [0.548, 0.796]</td>
</tr>
<tr>
<td>Fluid input (ml/h)</td>
<td>670 (53.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.649 [0.542, 0.755]</td>
</tr>
<tr>
<td>Urine output (ml/h)</td>
<td>670 (53.2)</td>
<td>&lt;0.001</td>
<td>0.206</td>
<td>0.602 [0.518, 0.686]</td>
</tr>
<tr>
<td>Fluid balance (ml)</td>
<td>656 (52.1)</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.596 [0.491, 0.701]</td>
</tr>
<tr>
<td>Creatinine (µM)</td>
<td>1250 (99.3)</td>
<td>0.027</td>
<td>&lt;0.001</td>
<td>0.666 [0.571, 0.761]</td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>1187 (94.3)</td>
<td>0.362</td>
<td>&lt;0.001</td>
<td>0.664 [0.572, 0.755]</td>
</tr>
<tr>
<td>Uric acid (µM)</td>
<td>1251 (99.4)</td>
<td>0.008</td>
<td>&lt;0.001</td>
<td>0.646 [0.552, 0.741]</td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total leukocyte count (x10⁹/L)</td>
<td>1257 (99.8)</td>
<td>0.089</td>
<td>0.004</td>
<td>0.635 [0.550, 0.721]</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L)</td>
<td>1255 (99.7)</td>
<td>-0.014</td>
<td>&lt;0.001</td>
<td>0.699 [0.609, 0.788]</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>1251 (99.4)</td>
<td>0.192</td>
<td>0.038</td>
<td>0.566 [0.481, 0.651]</td>
</tr>
<tr>
<td>Variable</td>
<td>N (%)</td>
<td>β-coeff</td>
<td>p</td>
<td>AUC ROC [95% CI]</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td>-------------------</td>
</tr>
<tr>
<td>MPV/plt ratio</td>
<td>1251 (99.4)</td>
<td>13.773</td>
<td>&lt;0.001</td>
<td>0.680 [0.586, 0.774]</td>
</tr>
<tr>
<td>INR</td>
<td>1133 (90.0)</td>
<td>12.615</td>
<td>&lt;0.001</td>
<td>0.717 [0.627, 0.807]</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>1134 (90.1)</td>
<td>0.041</td>
<td>0.001</td>
<td>0.684 [0.592, 0.776]</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>1035 (82.2)</td>
<td>-0.275</td>
<td>0.049</td>
<td>0.626 [0.516, 0.736]</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>1211 (96.1)</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.718 [0.635, 0.800]</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>1254 (99.6)</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.658 [0.557, 0.760]</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>1198 (95.2)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.621 [0.524, 0.718]</td>
</tr>
<tr>
<td>Bilirubin (µM)</td>
<td>1187 (94.3)</td>
<td>0.140</td>
<td>&lt;0.001</td>
<td>0.718 [0.627, 0.808]</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>1070 (85.0)</td>
<td>-0.139</td>
<td>&lt;0.001</td>
<td>0.695 [0.598, 0.791]</td>
</tr>
<tr>
<td>Random glucose (mM)</td>
<td>991 (78.7)</td>
<td>0.101</td>
<td>0.446</td>
<td>0.563 [0.468, 0.659]</td>
</tr>
<tr>
<td><strong>Fetal assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFI (DAP) (mm)</td>
<td>736 (58.5)</td>
<td>0.002</td>
<td>0.358</td>
<td>0.582 [0.465, 0.698]</td>
</tr>
<tr>
<td>EFW (%ile category)</td>
<td>669 (53.1)</td>
<td></td>
<td></td>
<td>0.624 [0.511, 0.738]</td>
</tr>
<tr>
<td>AC (%ile category)</td>
<td>693 (55.0)</td>
<td></td>
<td></td>
<td>0.658 [0.555, 0.762]</td>
</tr>
<tr>
<td>UA EDF (present, absent, reversed)</td>
<td>676 (53.7)</td>
<td>0.524</td>
<td>0.651</td>
<td></td>
</tr>
<tr>
<td>BPP (score /8)</td>
<td>191 (15.2)</td>
<td>13.487</td>
<td>0.995</td>
<td>0.613 [0.576, 0.650]</td>
</tr>
<tr>
<td>FHR (normal/suspicious/pathological)</td>
<td>1159 (92.1)</td>
<td>0.593</td>
<td>0.695</td>
<td>0.593 [0.491, 0.695]</td>
</tr>
</tbody>
</table>

* missing data filled assuming 97% (described in the Methods); † classified as 0, trace, 1+, 2+, 3+, 4+; 5 classified as 0.0-0.4%, 0.5-1.9%, 2.0-4.9%, 5.0-9.9%, 10.0-49.9%, 50.0-89.9%, 90.0-94.9%, 95.0-97.4%, 97.5-98.9%, ≥99.0% (44;45); ** using Royal College of Obstetricians and Gynaecologists definitions (46).

AC abdominal circumference; AFI amniotic fluid index; ALT alanine transaminase; APTT activated partial thromboplastin time; AST aspartate transaminase; BPP biophysical profile; DAP deepest amniotic fluid pocket; dBP diastolic blood pressure; EDD expected date of delivery; EFW estimated fetal weight (Hadlock); FHR fetal heart rate; GDM gestational diabetes mellitus; INR international normalised ratio; LDH lactate dehydrogenase; MAP mean arterial pressure; MPV mean platelet volume; preg pregnancy; RUQ right upper quadrant; SaO2 oxygen saturation (pulse oximetry); sBP systolic blood pressure; UA EDF umbilical artery Doppler end diastolic flow.
4.5 References


CHAPTER 5

Discussions and Conclusions

5.1 Principal findings

The ability to predict adverse maternal outcomes in pregnancies complicated by pre-eclampsia is highly relevant to clinical management. As discussed, the only definitive treatment for the maternal syndrome of pre-eclampsia is delivery (1), which, in cases of early-onset pre-eclampsia (GA<32 weeks’ gestation), is not the best option for the fetus (2;3). Thus, the priorities governing the maintenance of maternal health and fetal health in such pregnancies often conflict, and clinicians are often faced with the conundrum of timing delivery so as to minimize or avoid both maternal and fetal mortality and significant morbidities.

5.1.1 Severity criteria are not associated with adverse outcomes

At present, management of pre-eclampsia is guided primarily by clinical impression rather than by evidence-based criteria of disease severity. The major international guidelines (operational during the conduct of this study) for the diagnosis, evaluation and management of pre-eclampsia as published by Canadian (CHS in 1997 (4), updated recently by the SOGC in 2008 (1)), American (NHBPEP (5)) and Australasian (ASSHP (6)) associations, have several limitations, including being largely based on expert opinion rather than high quality evidence, and dichotomizing pre-eclampsia into either mild or severe disease, when in reality pre-eclampsia encompasses a
wider spectrum of disease. These guidelines also overlook other criteria which may be important predictors of maternal outcomes, the most apparent being gestational age (3;7).

Through interim analyses of the PIERS dataset, we have been able to demonstrate that the guidelines generated by the North American hypertension groups, the CHS and NHBPEP (4;5), recommend several criteria for disease severity that are not associated with adverse maternal outcome. Based on our data, many of these criteria should be reconsidered as indications for delivery of pregnancies remote from term (8). This finding is of great clinical importance, as the purpose of classification systems is to identify women at increased and decreased risk of developing complications. This is why clinicians use severity criteria as indications for delivery, as delivery is the only definitive treatment for pre-eclampsia.

Through this sub-study it was also noted that many of the items listed as severity criteria were not consistently performed or documented, as was the case for 24-hour urinary protein which was only collected in 47% of cases, leading to the added argument that these items fail to meet the recognized Richardson et al criteria for predictor variables, one of which is routine performance (9).

5.1.2 The developed PIERS models can predict maternal risk

In light of these identified challenges and shortcomings in the current guidelines for the management of pre-eclampsia, there is an identified need for a tool that can stratify women according to their individual risk of adverse outcome, in order to better inform those important clinical decisions surrounding timing and place of delivery. The research presented has sought to respond to that need by developing a system that takes
into consideration the systemic nature of the disorder of pre-eclampsia and that accurately predicts the occurrence of adverse maternal outcomes in pre-eclampsia pregnancies in a clinically useful fashion.

Through this research we have found that it is possible to develop an outcome prediction model for women admitted to hospital with a diagnosis of pre-eclampsia. Using readily available clinical data, two outcome prediction models, the Pre-eclampsia Integrated Estimate of RiSk (PIERS) models, have been developed and initially validated. Each of these PIERS models is able to identify women at increased (and decreased) risk of adverse maternal outcomes within 48 hours of, and up to 7 days after, a diagnosis of pre-eclampsia (eligibility), as demonstrated by their respective AUC ROCs.

The fullPIERS model, which incorporates 6 independent clinical and laboratory variables (chest pain/dyspnoea, SaO₂, dipstick proteinuria, platelet count, serum creatinine, and bilirubin) is intended for use in well-resourced settings where these tests are readily available. At 48h, this model performs extremely well with an AUC ROC of 0.906 [0.851, 0.961], and maintains good performance with AUC ROCs >0.7 out to 7 days.

The miniPIERS model incorporates 3 independent sign- and symptom-based variables (chest pain/dyspnoea, systolic blood pressure, and dipstick proteinuria), and is intended for use in minimally resourced settings, such as rural Canada and low and middle income countries (LMICs). At 48h, this model has an AUC ROC of 0.817 [0.738, 0.896], and also maintains AUC ROCs >0.7 out to 7 days.
5.1.3 Component variables included in the PIERS models

Face validity of the PIERS models has been achieved by the fact that the predictor variables included assess all the vulnerable organ systems afflicted by the syndrome of pre-eclampsia and that, when combined in a multivariate model, they predict a clinically important combined adverse maternal outcome with relatively high adequacy. Current physiology-based illness severity models have ROC areas of 0.7-0.9 (9). The PIERS models have achieved the upper end of that target range (fullPIERS AUC ROC = 0.906; miniPIERS AUC ROC = 0.817).

Measurement of proteinuria by dipstick is often criticized for its lack of sensitivity and specificity (10), but it is routinely utilized by practitioners (11) because it is a rapid, inexpensive, and readily available test. While assessment of proteinuria by 24-hour urine collections is the recognized “gold standard”, it was too infrequently performed in the PIERS cohort to be assessed (<50% of cases). It also has inherent problems with accuracy and reproducibility, with both over- and under-collections (12), and is, as its name implies, time-consuming leading to delays in clinical diagnosis (13). The spot urinary protein:creatinine ratio could be a viable alternative to the 24-hour collection (13), but it was also infrequently assessed (present in only 65% of cases) in the PIERS cohort. This is likely due to the fact that this method of assessment is relatively new to obstetrical practice and its frequency of use will likely increase as clinicians become more comfortable with its use and interpretation of results. Similar results were found in a feasibility study conducted by von Dadelszen et al in which the 24h urinary protein estimation was not measured frequently enough (21% of cases) to be evaluated, and where dipstick protein was identified as being a significant independent predictor of a
combined adverse maternal outcome in women admitted to tertiary care centres with pre-eclampsia (14). Thus, while dipstick proteinuria does violate the Richardson et al criteria of reliability it fulfills all others in that it is available, measurable, frequent and predictive (9).

The inclusion of symptoms in the final models (chest pain/dyspnoea) may also draw criticism in that they are not quantifiably measurable and, as such, may also not be reliable. However, they were assessed to maintain face validity, as there are data to suggest that they do have utility in the prediction of adverse maternal outcomes in pre-eclampsia (15) and they are included in several of the classification systems to define severe disease (1;4-6). Moreover, in an initial assessment of the data collected to date as part of the prospective re-validation study currently being conducted, the symptoms of chest pain and dyspnoea remain predictive of the adverse maternal outcome (data not presented).

All other predictor variables included in the final multivariate models (bilirubin, creatinine, platelet count and SaO₂) adequately fulfill all the Richardson et al criteria for item selection (9).

5.1.4 Component variables excluded from the PIERS models

There is the potential to have questions raised about the exclusion of a blood pressure component in the fullPIERS model, given that it is the elevation of blood pressure that is a critical component of the definition of the maternal syndrome of the disease. We suggest that the inability of blood pressure to maintain significance when included in a multivariable model is due to the fact that blood pressure is the only
component of the maternal syndrome that is readily treatable with effective antihypertensive medications (16) and, as such, its predictive value may have likely been diminished with the use of antihypertensive therapy. A comparison of the highest blood pressures recorded during the first 48h after eligibility revealed that there was no clinically significant difference between women who developed the combined adverse maternal outcome and those who did not, with only 4-10 mmHg differences in the blood pressure indices measured between the groups. However, in the sign- and symptom-based miniPIERS model, systolic blood pressure performs well, suggesting that the exclusion of other items that are likely more proximate to adverse outcomes than blood pressure (e.g. laboratory components) allows the predictive ability of blood pressure to reveal itself.

Another clinical variable traditionally considered important in the assessment of pre-eclampsia severity, but not included as a component of the final PIERS models, is aspartate transaminase (AST). Again, a comparison of the highest AST levels recorded during the first 48h after eligibility revealed that there was no clinically significant difference between women who developed the combined adverse maternal outcome and those who did not, with only a 4 IU difference measured between the groups. We suggest that a rise in bilirubin may occur more proximate to the occurrence of adverse outcomes than does a rise in AST, giving bilirubin a greater independent explanatory power and displacing AST in the multivariable modeling.

It must also be noted that neither of the PIERS models includes gestational age as a predictor of maternal outcomes, which was one of our earlier criticisms of the CHS (4), NHBPEP(5) and ASSHP (6) pre-eclampsia guidelines. While gestational age at
eligibility was significantly lower in those women who went on to develop one or more components of the combined adverse maternal outcome, it was not as strongly independently correlated with the combined outcome as other variables included in the modeling, and so could not retain a place in the model, as described in Chapter 4.

5.2 Strengths and limitations

5.2.1 Strengths attributed to the PIERS study

To our knowledge, this particular body of research has taken a very novel approach to outcome prediction in pre-eclampsia. It is the first international multi-centre study to successfully develop an outcome prediction model for women admitted to tertiary obstetric units with pre-eclampsia. The project was implemented as a continuous quality improvement initiative conducted on the premise of using a standardized approach for the initial assessment and ongoing surveillance of women admitted to these centres with pre-eclampsia. En route to the development of the PIERS models, we found that this systematic approach was associated with a significant reduction in the incidence of adverse maternal outcome (17), and identified that the NHBPEP (5) and 1997 CHS (4) definitions of disease severity poorly predict these outcomes, in women admitted with pre-eclampsia (8). The PIERS models were built using a prospectively collected, robust, error-checked dataset. Data were collected using customized case report forms (attached in Appendix B) and Microsoft Access™ database. Missing data and misclassification errors were minimized through rigorous database surveillance and random re-abstraction of charts to ensure accuracy.
One of the major differences between the PIERS approach to outcome prediction and that of the existing international guidelines lies in the way the candidate predictors are defined. The CHS (4) and NHBPEP (5) severity criteria are all dichotomized, using arbitrary cut-offs to define them (e.g. dBP ≥110 mmHg) (4;5). The approach undertaken by the PIERS research design allowed for candidate predictor variables to be analysed either continuously or categorically, as appropriate, to allow for better discrimination of the relationship between the predictors and the combined adverse maternal outcome. Another notable difference is that, in contrast to the classification systems outlined in the aforementioned international guidelines which are based mainly on retrospective diagnosis, the PIERS models have been developed using clinical data available at presentation, when plans for management are made.

This programme of research is also of high clinical relevance to the management of women with pre-eclampsia. Prior to the development of the PIERS models, there was no evidence-based system in existence that had been related to quantifiable maternal risk for adverse outcome. By having the ability to group women according to the risk of adverse maternal and perinatal outcomes that make pre-eclampsia so important, the PIERS models will allow clinicians to stratify maternal risk in real-time to advise clinical decision-making by women, their families and their caregivers.

### 5.2.2 Limitations attributed to the PIERS study

There are some limitations to this study.

Firstly, there were some problems with missing data, particularly in the categories of urine protein assessments (24h urine collections and spot protein:creatinine urines) and
in fetal ultrasound assessments (amniotic fluid index, estimates of fetal weight and umbilical artery Doppler), which were only present in \( \leq 65\% \) of cases. Despite the fact that these components were included as required assessments on the pre-printed standing orders (or their equivalent protocols) in each centre and monitored by ongoing audit, they were not performed with adequate frequency to be included in the modeling. Thus, it is highly unlikely that these variables would be performed in routine clinical practice in the “real world” where such protocols and monitoring are not in place, and, as such, may not have a place in predictive models for the complications of pre-eclampsia.

Secondly, the PIERS models were developed and initially cross-validated using a single data set, which prevents us from accounting for time and changes in practice. Furthermore, the study was conducted in tertiary obstetric units in high-income countries in women who fulfilled a research definition of pre-eclampsia. This impairs the ability to generalize the PIERS models to other clinical settings (as is certainly the case for the miniPIERS model) and for the other hypertensive disorders of pregnancy.

The PIERS models were also developed using a relatively small sample size, especially when taking into account the low incidence of the adverse maternal outcomes within the cohort (3.3\% and 7.1\% within 48h and 7d respectively).

These aforementioned limitations are currently being addressed through a Canadian Institutes of Health Research (CIHR) and World Health Organization (WHO) funded re-validation study taking place in new cohorts of women in both high and low risk obstetric units in high, middle and low income country settings, in women with either pre-eclampsia or any other hypertensive disorder of pregnancy (including chronic hypertension and gestational hypertension without proteinuria).
Finally we have not been able to compare the developed PIERS models directly against the existing classification guidelines [CHS (4), NHBPEP (5), ASSHP (6)] or other analogous outcome prediction models [(APACHE (18), MOD (19), Brussels (20) scores]. In the cases of the aforementioned guidelines, we have shown that a direct comparison would not be possible due to the fact that many of the “severity criteria” intrinsic to these dichotomous classification systems are either not available (e.g. 24 hour urinary protein), or not predictive (e.g. visual disturbances), and those few that are predictive are often co-linear (e.g. ‘elevated liver enzymes’ and HELLP syndrome) (8). In the cases of the latter described prediction models, a direct comparison would be unattainable due to the fact that several elements in these models are not generalisable or clinically acceptable to clinicians working in the realm of pre-eclampsia. For example the variables to assess oxygenation, alveolar-arterial oxygen gradient (A-aDO₂) or partial pressure of arterial oxygen (PaO₂), used in APACHE (18) requires measurement of arterial blood gases, which are only assessed in very sick patients admitted to intensive care/high-dependency units. However, as most pre-eclampsia is mild and develops at term these women would not require such assessments. It has also been demonstrated that when used to predict mortality among eclamptic women in an ICU setting, APACHE did not perform well (21).
5.3 Comparisons with relevant studies

5.3.1 Utilizing the APACHE II illness severity score in the setting of eclampsia

Previous research to evaluate the use of existing predictive models in the setting of the pre-eclampsia/eclampsia syndrome have revealed “…the need for a tailored scoring system that more accurately predicts the maternal mortality of those conditions peculiar to pregnancy” (22). The use of the APACHE II score to predict mortality in women admitted to an intensive care unit with eclampsia revealed that most of the variables evaluated in the APACHE II score, other than the Glasgow Coma Score, were not useful predictors and that the APACHE II score tended to predict mortality that did not, in fact, occur (21). While the APACHE II score is designed to predict mortality in patients admitted to intensive care unit settings with the systemic inflammatory response syndrome (SIRS), which pre-eclampsia has been noted to bear a significant resemblance to (23;24), it was developed using a cohort of non-pregnant, typically elderly patients with significant chronic illnesses (22;25). Thus it is not entirely surprising that it is not generalisable to the disorder of pre-eclampsia, which afflicts pregnant women who are relatively young, and otherwise healthy outside of pregnancy, and for whom mortality is actually a rare event (22;26). There are also significant morbidities associated with pre-eclampsia with evaluative physiologic variables that are not accounted for in the APACHE II score, for example bilirubin or aspartate transaminase (AST) as indicators of hepatic function (or dysfunction) (22;25). In comparison, the PIERS models have been developed against a combined adverse maternal outcome, which also includes those significant morbidities that have been deemed by clinicians as being significant enough to be worthy of avoidance, even in the face of extreme prematurity (14). The PIERS study
design (described in Appendix A) also utilized a standardized approach to evaluate those clinically relevant investigations that evaluate vulnerable organ function (or dysfunction) in the multiple systems known to be affected by the syndrome of pre-eclampsia (14).

5.3.2 Previous studies attempting to develop outcome prediction models specific to pre-eclampsia

Previous attempts to devise an outcome prediction model specifically for women with pre-eclampsia have also not been successful.

von Dadelszen et al attempted to do so using a multi-centre retrospective chart review, and, while they were able to reveal several promising variables, including dipstick proteinuria, for the prediction of adverse outcome, they were limited by a small sample size (n=594) and also experienced problems with missing data which left them underpowered to adequately assess the utility of many of the candidate variables they had initially chosen to investigate (14). However, this study did prove feasibility for the development of a predictive model for pre-eclampsia, and suggested the need for a larger study utilizing prospective data collection to ensure adequate availability of all candidate predictors. These findings guided the design for the PIERS body of research, in which a prospective, standardized approach of continuous quality improvement (CQI) with standing orders was undertaken (described in Appendix A).

Ganzervoort et al endeavoured to use clinical parameters assessed at admission, in women with hypertensive complications of pregnancy remote from term (i.e. gestational age between 24-34 weeks), to predict major maternal complications arising at any point during the course of that admission, and found that they were unable to do so (27). The
cohort used by Ganzevoort et al for their investigation was different from that used for PIERS, in that it was comparatively small (n=216) and the women included were initially enrolled in an open-label randomized controlled trial investigating the use of plasma volume expansion during the practice of expectant management to improve maternal and fetal outcomes in women with early-onset hypertensive complications of pregnancy (27). The inclusion criteria for the trial were also slightly different: in addition to HELLP syndrome and severe pre-eclampsia (which are also inclusion criteria for PIERS), they included women with eclampsia (considered a component of the PIERS combined adverse maternal outcome), and women with fetal growth restriction with pregnancy-induced hypertension (not considered in PIERS) (27).

Many of the clinical predictors investigated by Ganzevoort et al were also investigated in the PIERS study, including maternal age, parity, ethnicity, body mass index, gestational age, estimated fetal weight, and blood pressure. Additional parameters investigated that were not included in PIERS were antihypertensive medication, pulse rate, hemoglobin concentration, admitting centre (of the trial), diagnosis at inclusion, chronic hypertension and thrombophilia (27). However, Ganzevoort et al also dichotomized many of the continuous parameters investigated, using the median value as the cut-point. For example, diastolic blood pressure as a predictor was considered as being either “non-high” (<105 mmHg) or high (≥105 mmHg) (27). In contrast, the PIERS study considered candidate predictors as continuous variables wherever possible, to allow for better discrimination of the relationship between the predictors and the combined adverse maternal outcome.
The composite adverse maternal outcome that Ganzevoort et al sought to predict, was also slightly different that that of the PIERS study. In addition to a few components also investigated by the PIERS study [pulmonary oedema, hepatic haematoma, severe renal insufficiency, encephalopathy and cerebral haemorrhage (captured as other severe neurological events in PIERS)], they also included placental abruption, severe infectious morbidity (sepsis), severe thrombotic morbidity (pulmonary embolism or catheter-associated thrombosis), new or recurrent HELLP syndrome, and new or recurrent eclampsia after inclusion (27).

The best prediction model achieved for adverse maternal outcome demonstrated very poor discrimination, with an AUC ROC of only 0.65 and included only low estimated fetal weight (EFW below median 1100g) and nulliparity, neither of which were included in the PIERS models (27). This inability to predict outcomes occurring at anytime following admission is also what we found to be true when conducting the PIERS modeling, where performance of the most parsimonious fullPIERS and miniPIERS models deteriorated significantly (AUC ROCs <0.7) after 7d post-eligibility. This is likely due to the fact that pre-eclampsia is a disease in evolution which continues to evolve post-admission/eligibility and there comes a critical point where the component predictors of the models are no longer proximate enough to the occurrence of the outcome to retain their prognostic abilities. However, the ability of the PIERS models to predict adverse outcomes with adequate discrimination from 48h-7d post-eligibility, will allow clinicians and patients to make better informed decisions surrounding timing of delivery and place of care, as this is the time frame in which these decisions are typically made.
Another similarity between the two studies is that gestational age was not found to be correlated with the maternal complications each study sought to predict, and was not an included component in any of the final multivariate prediction models created (27). This finding opposes that of Haddad et al who observed that, in women with HELLP syndrome, gains in gestational age resulted in a significantly decreased incidence of eclampsia (28). However they also found that, other than for rates of Caesarean delivery, gestational age differences did not correlate with any statistically different rates in any of the other adverse maternal outcomes considered (28), which included several of the maternal morbidities considered by Ganzevoort et al (27) and listed in the PIERS defined combined adverse maternal outcome, such as pulmonary oedema, acute renal failure, liver haematoma and need for transfusion of blood products. As eclampsia is only one component of the respective combined adverse maternal outcomes defined in the Ganzevoort et al (27) and PIERS studies, gestational age has most likely been replaced in these models by predictors more closely correlated with the development of the overall combined outcomes.

### 5.4 Implications and applications for clinicians and researchers

After development and initial validation, the PIERS models have demonstrated the ability to predict adverse maternal outcomes up to 7 days before complications arise. This ability to identify those women at increased (and decreased) risk of maternal mortality and/or significant morbidity, has important clinical relevance in terms of providing clinicians with information to better advise them of the appropriateness of practicing expectant management, and to allow them to better coordinate the timing and
place of delivery. It is well known that, remote from term, each additional day that a fetus is able to remain in utero allows for improvements in perinatal outcomes (2;3), and utilization of the PIERS models to identify women who are appropriate for pregnancy prolongation will potentially minimize both iatrogenic prematurity (thus improving child health) as well as the maternal risks associated with pre-eclampsia.

The PIERS prediction models may also advise the design, conduct and analysis of future health services and basic science research and randomized controlled trials, by allowing investigators to classify women into meaningful sub-groups associated with the spectrum of disease severity and differential maternal risk. In doing so, the PIERS models may contribute to improvements in the understanding of the pathophysiology of pre-eclampsia, which may in turn lead to the development of new treatments and interventions designed to further reduce maternal and perinatal morbidity and mortality. The PIERS models may also advise health policy and resource allocation, as those investigations that best predict outcomes are identified while others, that have not been found to be informative for patient care, may be abandoned.

5.5 Conclusion

In conclusion, we have successfully developed and initially validated 2 outcome prediction models (fullPIERS and miniPIERS) specific to the condition of pre-eclampsia, each with the ability to predict adverse maternal outcomes up to 7 days before complications arise. This capability of the PIERS models to identify those women at increased (and decreased) risk of the adverse maternal outcomes that make pre-eclampsia so important, will provide clinicians with an additional tool to facilitate more informed
management of pregnancies complicated by this disorder, potentially leading to improvements in maternal and perinatal health.

5.6 Future directions

5.6.1 Re-validation of the PIERS models

The PIERS models are currently being re-validated through another prospective international study in both high (for the fullPIERS model, with funding support from the CIHR) and low to middle income (for the simplified miniPIERS model, with funding support from the WHO) countries, in women admitted to both high and low risk obstetric units with pre-eclampsia as well as the other hypertensive disorders of pregnancy. This will allow us to determine the generalisability, sensitivity, specificity, predictive values and accuracy of the model in numerous jurisdictions and across all conditions considered in the realm of the hypertensive complications of pregnancy.

5.6.2 Development of the PIERS scoring system

Once these models have been re-validated, we must undertake the development of a PIERS scoring system, in which each predictive variable in the models are appropriately weighted according to their respective $\beta$-coefficients retained in the final multivariate logistic regression models. In logistic regression, the $\beta$-coefficient of a variable represents the log odds ratio that that variable is associated with the outcome, independent of the other variables in the model (9). That is, a variable with a high $\beta$-coefficient is more predictive of the outcome than one with a low $\beta$-coefficient. Thus the $\beta$-coefficients can be used to assign PIERS model points, a score weight for each
variable, so that its contribution to overall prediction of the outcome is proportionate (9). This empiric method of assigning item weights was utilized in the re-validation of both the SNAP II (29) paediatric and APACHE III (18) adult intensive care scoring systems (9). The numerical PIERS score will be reflective of the overall predicted risk of the combined adverse maternal outcome as determined by the level of perturbation of the components of the laboratory and/or clinical components of the models.

It would also be prudent to test the ability of the PIERS models to detect change whereby, as a woman’s clinical condition worsens or improves, so would her assessed PIERS score. This could be done by utilizing the method of Lee et al (30), in which we will stratify women into four categories with increasing PIERS points to determine whether decreases or increases in score category will be associated with fewer or more maternal outcomes, respectively, than if the score were unchanged.

5.6.3 Implementation of the PIERS models into routine clinical use

Once re-validation is complete and a PIERS scoring system has been created, the PIERS models must be methodically introduced into routine clinical use at all levels of care. Usually, randomized controlled trials (RCTs) are the standard strategy for the implementation of changes to clinical practice. However we feel that to conduct an RCT for the implementation of the PIERS models would raise significant ethical concerns, as this would require that utilization of the models, which we believe to be an effective intervention, be withheld from half of the eligible population. As such, we believe that the implementation of the PIERS models may be best achieved using a step-wedge design, in which the models (i.e. the change in clinical management) are introduced into
centres at different intervals and where the incidence of adverse maternal outcomes is closely monitored to determine the actual impact of the PIERS models. If the PIERS models are indeed effective interventions, then a step-wise reduction in the incidence of the combined adverse maternal outcome should occur as each centre introduces the intervention, and such a fall should be noted within each site.

5.6.4 Economic analyses

It may also be worthwhile to conduct an assessment of economic implications of utilization of the PIERS models. The ability of the models to identify pregnancies which can be both reasonably prolonged and also managed in local obstetric units will allow for more apt decisions regarding appropriateness of place of care and timing of transfers, thus reducing the maternal risks and costs associated with both unnecessary transfers or inappropriately delayed transfers. This will also improve child health and minimize the paediatric costs associated with iatrogenic prematurity. The development and validation of the PIERS models also has cost-saving implications at the laboratory level, by identifying those assessments which are most predictive of adverse maternal outcomes, and also those investigations that are either highly correlated and therefore redundant when performed together, or have not been found to be informative and thus may be abandoned from routine surveillance.
5.6.5 Development of a perinatal outcome prediction model

Finally, both the fullPIERS and miniPIERS models designed for the purposes of maternal outcome prediction, have not performed well when used to predict adverse perinatal outcomes (AUC ROCs < 0.7). This finding indicates the need for a separate perinatal model to be created to predict the specific perinatal risks in pregnancies complicated by the hypertensive disorders. There are current plans to conduct a separate study to develop the WILL (When is Intact Livebirth Likely) model for the purposes of perinatal outcome prediction.
5.7 References


Appendix A

Detailed Methodologies

A1 Study Design

A1.1 Sites

Participants were recruited from seven academic tertiary maternity hospitals in Canada, the United Kingdom, New Zealand and Australia:

1. BC Women’s Hospital and Health Centre (BCWHHC, Vancouver, BC)
2. Le Centre hospitalier universitaire de Sherbrooke (CHUS, Sherbrooke, Quebec)
3. Kingston General Hospital (Kingston, Ontario)
4. Ottawa General Hospital (Ottawa, Ontario)
5. Leeds Teaching Hospitals NHS Trust (Leeds, UK)
6. Christchurch Women’s Hospital (Christchurch, New Zealand)
7. King Edward Memorial Hospital (Subaico, Western Australia) [joined study in July 2006]

Data were collected prospectively at each of these seven sites using a standardized approach. All of the participating centres have a general policy of expectant management of pre-eclampsia remote from term.

Ethics approval to conduct the PIERS international study was granted by the University of British Columbia Clinical Research Ethics Board (Appendix C).
addition, ethics approval to conduct the study was obtained from the governing research ethics board overseeing each individual site.

A1.2 Inclusion/Exclusion criteria

Women with suspected or confirmed pre-eclampsia were included in the study if they met the following inclusion/exclusion criteria:

**Inclusion criteria:**

These criteria reflect the evidence that pre-eclampsia is more than hypertension and proteinuria (1-4), particularly at onset:

- **Hypertension.** Systolic BP (sBP) ≥140mmHg and/or diastolic BP (dBP) ≥90mmHg, twice, ≥4h apart after 20 weeks' gestation, by any method in hospital and either
  - **Proteinuria.** 24h urinary protein ≥0.3g/d (5), or in the absence of a 24h urine collection: ≥2+ dipstick proteinuria or a random protein:creatinine ratio ≥30mg protein/mmol creatinine (6-12) after 20 weeks’
  - **Hyperuricaemia.** Uric acid/urate levels above the upper limit of the normal non-pregnancy range for local laboratory.

**OR**

- **HELLP (haemolysis, elevated liver enzymes and low platelet) syndrome** with or without hypertension and/or proteinuria (13)

**OR**
• **Superimposed pre-eclampsia** (5;14;15) defined as a history of **pre-existing hypertension** with either:

  • **new proteinuria:**

    - 24h urinary protein $\geq 0.3$g/d, or
    - $\geq 2^+$ dipstick proteinuria, or
    - a random protein:creatinine ratio $>30$mg protein/mmol creatinine after 20 weeks’ gestation

  or

  • **new hyperuricaemia**: Uric acid/urate levels above the upper limit of the normal non-pregnancy range for local laboratory.

  or

  • **accelerated hypertension**:

    - rapidly increasing requirements for antihypertensives, or
    - sBP $>170$ mmHg and/or dBP $>120$ mmHg, or
    - diagnosis/clinical impression as documented by the clinician

**Exclusion criteria:**

• Occurrence of the maternal outcome **prior to** collection of the predictors.

• Occurrence of the maternal outcome **prior to** fulfilment of eligibility criteria.

• Admission to hospital in **spontaneous labour** (as clinicians will not attempt to stop these labours).
A1.3 Standing orders

As part of the process to develop a clinical prediction model for pre-eclampsia, a single site pilot study (data not presented) was conducted at the BC Women’s Hospital and Health Centre (BCWHHC). Initially, at this centre women were approached for their explicit consent to follow a standardized set of clinical and laboratory assessments for the assessment and surveillance of their condition and to allow for the inclusion of their clinical data into the database which would be utilized to derive the model. However, it was soon discovered that those women who were most unwell, and therefore, most likely to develop the outcome against which the model would be developed, were the least likely to consent because of the stresses of their situation. They also tended to have at least as much blood work performed as the study protocol initially called for. It had also been previously established that a predictive model could not be developed using a retrospective chart review, due to the variability in the assessment and monitoring of women with hypertensive disorders of pregnancy among clinicians (16) and missing data points (4).

Therefore, we moved to changing local practice through a continuous quality improvement (CQI) initiative, in which standardized guidelines to advise practice during the initial assessment and ongoing surveillance of women admitted to hospital with either pregnancy hypertension and/or proteinuria were introduced into routine clinical care, with the intent of including a subset of these women in the development set for the prediction model. This CQI approach received the support of the hospital administration and all relevant clinical services at BCWHHC, and the approval of the local governing ethics boards (UBC CREB and C&W).
This continuous quality improvement (CQI) initiative began with the introduction of these guidelines into practice at BCWHHC in September 2003 through the North American practice of standing orders. Standing orders are pre-printed forms used to standardize management to improve outcomes. These standing orders were introduced as a minimum standard for care. The timing of the investigations is at least as frequently as on admission, admission +1, and then every Monday and Thursday until delivery. Postpartum, the investigations are performed on day of delivery, delivery +1, then every Monday and Thursday until discharge. The attending clinician was free to repeat any of the investigations at additional times that a woman’s disease was felt to be deteriorating.

### A1.4 Selection of candidate predictor variables

To reflect the variable presentation and systemic nature of pre-eclampsia (1-3), the standing orders include multi-system investigations that evaluate comprehensively vulnerable organ function (or dysfunction) in the following systems:

**Maternal**

1. **Cardiovascular:** maternal blood pressure
2. **Renal:** urea, creatinine, and uric acid. Urine is assessed by dipstick and random urine for protein:creatinine ratio, and by 24h urine for protein and creatinine clearance (on admission and once weekly)
3. **Haematology:** full blood screen (mean platelet volume (MPV), platelet count and MPV:platelet count ratio), international normalized ration (INR), activated partial thromboplastin time (aPTT), and fibrinogen
4. **Hepatic**: aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), bilirubin, albumin (plasma), and random glucose

5. **Respiratory**: pulse oximetry

**Fetal**

6. **Fetal surveillance** (antenatally only): cardiotocography (CTG) and ultrasound for assessment of fetal weight, amniotic fluid volume and umbilical artery Doppler.

These standing orders were derived from the pattern of investigation used in other centres of excellence, in response to international guidelines (5;14;15), to current practice across Canada (16), and by an international Delphic consensus conducted in 2001 (17;18).

These particular standing orders were adopted by one other participating site. All other sites utilized equivalent local standard protocols for the assessment and surveillance of their patients admitted with suspected or confirmed pre-eclampsia. The study was approved to be conducted as a continuous quality improvement (CQI) project (i.e. no informed consent process required), by the local ethics boards at three sites. At the other four sites informed consent was required to allow for data collection, data sharing and/or follow-up at 6 weeks post-partum as per the local ethics committee requirements.

In addition to the above listed tests, data were collected on various demographics (e.g. gestational age, parity), past obstetric history (e.g. gestational hypertension in a previous pregnancy), past medical history (e.g. pre-existing renal disease), family history (e.g. hypertension), and symptoms (e.g. frontal headache, visual disturbances) thought to be important clinical indicators in the setting of pre-eclampsia.
The candidate predictor variables assessed have been selected on the basis of five criteria, as described by Richardson et al (19). The items selected fulfilled most, if not all, of the following criteria:

1. Predictive (i.e. they correlate with the outcome of interest)
2. Available
3. Measurable
4. Frequent
5. Reliable

It is recognized that symptoms are not quantifiably measurable and, as such, may also not be reliable, however they were assessed to maintain face validity, as there is data to suggest that they do have utility in the prediction of adverse maternal outcomes in pre-eclampsia (20) and they are included in several of the classification systems to define severe disease (5;14;15).

A full list of all variables investigated (n=73) were provided in Table 4.1 of Chapter 4.

A1.5 Combined adverse maternal outcome

The combined adverse maternal outcome that the PIERS model aims to predict within 48 hours of fulfilling the eligibility criteria for the study definition of pre-eclampsia was initially defined as follows:

- **Initial definition:**
  - Maternal mortality, or one/more of:
    - **Hepatic:** hepatic failure, haematoma or rupture;
**CNS:** Glasgow Coma Score (GCS) <13, stroke, 2 or more eclamptic seizures, cortical blindness;  

**Renal:** dialysis or transplantation;  

**Cardiovascular:** positive inotrope support; infusion of nitroprusside, GTN, or diazoxide; and myocardial infarction;  

**Respiratory:** required ≥50% O₂ for >1hr, intubation;  

**Haematological:** transfusion of ≥ 10U blood products (any)

This combined maternal outcome was also derived by the international Delphic consensus (17;18) conducted in 2001, and was developed to reflect the multi-system nature of pre-eclampsia. The list is based on known end organ complications for pre-eclampsia that would change clinical management by being considered worthy of avoidance even in the face of extreme prematurity of the fetus.

This list was revised after an Investigators’ Meeting held in Vancouver, British Columbia on July 21-22, 2004. All co-investigators from the original six sites involved in the PIERS project were in attendance, as well as some of the site study co-coordinators. At this meeting, preliminary data obtained from BCWHHC was presented, in which it was noted that a considerable reduction in the incidence of the adverse maternal outcome (from 5.1% to 1.2%) had occurred since the introduction of the standing order guidelines for the assessment and surveillance of women admitted to that centre with a hypertensive disorder of pregnancy (21). As a result of this meeting and the discussions that ensued, it was felt that the above listed combined adverse maternal outcome was comprised of rare outcomes and that less severe outcomes would also be of clinical relevance by being considered worthy of avoidance, even at early gestational
ages. Thus, to reflect this, the following changes to the combined maternal outcome were made to maintain the feasibility of completing the study with the allocated resources while still maintaining the clinical relevance of the combined outcome to be predicted (changes identified in **bold** font):

- **Revised definition:**

  Maternal mortality, or one/more of:

  **Hepatic:** hepatic dysfunction or failure; hepatic haematoma/rupture;

  **CNS:** Glasgow Coma Score (GCS) <13, stroke, **eclampsia**, cortical blindness;

  "other" **adverse neurological events** (e.g. reversible ischaemic neurological deficit (RIND), retinal detachment, posterior reversible encephalopathy);

  **Renal:** acute renal failure; dialysis;

  **Cardiovascular:** positive inotrope support; infusion of a 3rd parenteral antihypertensive; and myocardial **ischaemia**/infarction;

  **Respiratory:** pulmonary oedema; requirement for ≥50% O_2_ for >1hr; intubation (other than for Caesarean section);

  **Haematological:** transfusion of any blood product(s);

  **Other adverse events:** free text category added to allow for the collection of other adverse maternal events that may occur in relation to the course of pre-eclampsia, deemed as being clinically relevant through iterative discussions between the relevant site investigator and the principal investigator.

Each of these components of the combined adverse maternal outcome is more thoroughly defined below:
• Hepatic dysfunction/failure
  
  o In the absence of disseminated intravascular coagulation (DIC) or treatment with Warfarin: INR >1.2.
  
  o In presence of DIC or Warfarin treatment: mixed hyperbilirubinaemia (>17µM) or hypoglycaemia (<2.5mM) in the absence of insulin.

  ▪ For the hypertensive pregnancy population, DIC is defined as both
    
    (1) Abnormal bleeding
    
    and
    
    (2) Consumptive coagulopathy (i.e., low platelets (< 100 x 10^9/L), abnormal peripheral blood film of microangiopathic changes, OR one/more of the following: increased INR (international normalized ratio), increased PTT (partial thromboplastin time), low fibrinogen, or increased FDP (fibrin degradation products) that are outside the normal non-pregnancy ranges for your hospital.

• Hepatic haematoma or rupture: presence of blood collection under the hepatic capsule as confirmed by ultrasound or at laparotomy.

• Glasgow coma scale (GCS) <13: The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. A GCS of ≥13 correlates with a mild brain injury, 9 to 12 with a moderate injury, and ≤8 with a severe brain injury. The GCS is composed of three parameters: best eye response, best verbal response, and best motor response.
- Best eye response is scored as: no eye opening (1), eye opening to pain (2), eye opening to verbal command (3), and eyes open spontaneously (4).
- The best verbal response is scored as: no verbal response (1), incomprehensible sounds (2), inappropriate words (3), confused (4), and orientated (5).
- Best motor response is scores as: no motor response (1), extension to pain (2), flexion to pain (3), withdrawal from pain (4), localizing pain (5), and obeys commands (6).

- Stroke: acute neurological event with deficits lasting greater than 48 hours
- Eclampsia: any eclamptic seizure
- Cortical blindness: loss of visual acuity in the presence of an intact pupillary response
- Other adverse neurological events: specify (e.g. reversible ischaemic neurological deficit (RIND), retinal detachment, posterior reversible encephalopathy)
  - Reversible neurological deficit (RIND): transient neurological deficit lasting less than 48hr
  - Retinal detachment: a separation of the inner layers of the retina from the underlying pigment epithelium (RPE, choroid) and is diagnosed primarily by opthamological exam
- Acute renal failure: creatinine >200µM
- Dialysis: includes haemodialysis or peritoneal dialysis
• Positive inotropic support: use of vasopressors to maintain a sBP >90mmHg or a mean arterial pressure >70mmHg

• Infusion of a third injectable antihypertensive: indication of infusion of a 3rd injectable antihypertensive (nitroprusside, nitroglycerine/glyceryl trinitrate (NTG/GTN) and/or diazoxide) because of uncontrollable hypertension, as per the hospital chart

• Myocardial infarction: any one of:
  o Typical rise and fall of biochemical markers of myocardial necrosis (troponin or CK-MB) with at least one of the following: a) ischaemic symptoms; b) new pathological Q waves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty);
  or
  o New pathologic Q waves on serial ECGs, with or without symptoms, with/without elevated biochemical markers of myocardial necrosis;
  or
  o Pathological findings of a healed or healing MI.

• Myocardial ischaemia: ECG ST segment elevation/depression without enzyme changes

• Pulmonary oedema: clinical diagnosis AND one or more of O₂ saturation <95%, diuretic treatment, or X-ray confirmation

• Requirement of ≥50% O₂ for >1hr.
• Intubation: ventilation by endotracheal tube, or non-invasively by continuous positive airway pressure, other than for Cesarean section

• Transfusion of any blood product

• Other adverse maternal events: any other adverse maternal events occurring in relation to the course of pre-eclampsia that local investigators feel is severe enough to note

A1.6 Combined adverse perinatal outcome

A combined perinatal outcome was also defined and collected as a secondary outcome and included the following components, which did not change over the course of the study:

• Bronchopulmonary dysplasia (BPD): defined as oxygen requirement at a postnatal gestational age of 36 completed weeks and chest x-ray compatible with BPD (22)

• Cystic periventricular leukomalacia: defined as periventricular cystic changes in the white matter, excluding sub-ependymal and choroid plexus cysts, diagnosed on or before hospital discharge, by cranial ultrasound or at autopsy

• Infant mortality: defined as death within the first year of life

• Intraventricular hemorrhage: grade III or IV, as defined by Papile et al (23)

• Necrotizing enterocolitis (NEC): defined according to Bell’s criteria (stage 2 or higher), diagnosed by x-ray, surgery, or at autopsy (24)

• Neonatal mortality: defined as death of a newborn until hospital discharge
• Retinopathy of prematurity (ROP): stage 3 to 5 in one/both eyes (intraretinal ridge with extraretinal fibrovascular proliferation, or retinal detachment (25))

• Stillbirth: defined as death of a fetus at \( \geq 500 \text{g} \) or at \( \geq 20 \) weeks gestation

A2 Data

A2.1 PIERS case report form development

The customised case report forms (CRFs) created specifically for data entry for the PIERS project began with a very basic preliminary version (v1.1), based on the information we hoped to be able to publish at the end of the study. The PIERS case report forms were utilized by all participating sites and consist of four segments:

Segment 1: Maternal—Day of First Admission.

This segment was designed to be completed as soon as a woman was deemed eligible for participation in the study. It consisted of six sections pertaining to admission details and patient history.

Section A: Admission information

Section B: Identifiers

Section C: Previous adverse pregnancy outcomes

Section D: Medical history

Section E: Family history

Section F: Treatment during this pregnancy
Segment 2: Clinical Assessments and Labs.

This segment consisted of three tables and was meant to collect the results of all relevant maternal and fetal clinical assessments and laboratory investigations.

Table 1: Clinical Assessments
Table 2: Maternal Lab Investigations
Table 3: Fetal Assessments

Segment 3: Maternal Outcomes/Delivery.

This segment consisted of four sections and was designed to collect information pertaining to events occurring during a woman’s admission to hospital.

Section A: Events during course of pregnancy
Section B: Adverse maternal outcomes
Section C: Delivery
Section D: Events after delivery

Segment 4: Neonatal Outcomes.

This segment was designed to collect information pertaining to birth details and adverse neonatal outcomes.

While the essential framework of the CRFs did not change, the content evolved through 15 different versions. The changes in each version of the CRF were made as a result of:
• Consultations with study Principal Investigator and research supervisor, Dr. Peter von Dadelszen, a respected and experienced perinatologist, and Dr. Laura Magee, an obstetric internist, both of whom specialize in the hypertensive disorders of pregnancy and provide a wealth of clinical knowledge.

• The July 2004 Investigators Meeting: A meeting held in Vancouver, British Columbia on July 21-22, 2004. All co-investigators from the original 6 sites involved in the PIERS project were in attendance, as well as some of the site study co-coordinators. As a result of this meeting and the discussions that ensued, the following most important changes to the data collection forms were recommended and implemented into Version 1.13:
  o Recording booking or pre-pregnancy blood pressure
  o Allowing for collection of data from the immediate pre-admission period and/or from other institutions prior to transfer
  o Collecting both the systolic (sBP) and diastolic (dBP) components of highest blood pressures in order to be able to calculate mean arterial pressure (MAP), as this is a better indicator of perfusion pressure seen by organs than either sBP or dBP alone.
  o Recording of all blood products received, including type and number of units transfused, and reason for transfusion
  o Re-defining the list of adverse maternal outcomes (as outlined previously)
  o Collecting complications due to analgesia or anaesthesia
  o Collecting highest blood pressures recorded antepartum, intrapartum and postpartum on day of delivery in order to distinguish high blood pressures
recorded during labour from those recorded in the immediate ante- and post-partum periods.

- The September 2005 teleconference: A teleconference with PIERS co-investigators and study co-coordinators from the other five participating sites was held on September 14, 2005. This teleconference was initiated due to a lower recruitment rate than anticipated and was meant to trouble-shoot this problem. Certain sites commented on the fact that most of their women with “mild” pre-eclampsia were managed as outpatients rather than inpatients and, as a result of the requirement for PIERS participants to be “admitted to hospital”, were often missing these potential recruits. It was decided between the co-investigators, that these women were also of interest in the context of the PIERS project, as these pregnancies were complicated enough to warrant close monitoring in an outpatient setting, and should be included in the data set. Therefore it was necessary to add the following elements to the data collection forms to allow for the collection of outpatient data:
  - Collecting information pertaining to whether patient was recruited to the study as an outpatient or an inpatient
  - Collecting the date that pre-eclampsia was first diagnosed, if diagnosed as an outpatient prior to first admission
  - Creating a separate and specialized set of forms (Maternal Outpatient Management Insert Forms) for collection of outpatient data. These forms consist of a condensed version of the full data collection form, and include only those components applicable to outpatient management.
These additions resulted in CRF Version 1.15, which was the current and final version of the PIERS data collection form. A copy of this final CRF is attached as Appendix B.

A2.2 PIERS database development

A customised Microsoft Access® database was created by the PIERS data manager, Larry Li, and was based on the PIERS case report forms. The first version of this database was created using Version 1.9 of the CRF. The database evolved along with the next six versions of the CRFs, and the current database contains all the data fields found in Version 1.15. The database was designed to flow in the same manner as the CRF to facilitate speedy and simple data entry. All seven sites involved in the PIERS project utilized this database for entry of data collected on the paper CRF into electronic form.

A2.3 Data collection

All data collectors at each of the 7 participating sites received detailed instruction regarding the working protocol to be followed when collecting data for the PIERS project, and are stable members of their local pre-eclampsia research groups. Data were collected commencing from a woman’s first admission for suspected or confirmed pre-eclampsia, and continued until her final postpartum discharge from hospital. For each of the data points, if more than one result is available on a given date, then the most abnormal result for that 24h period was recorded, as was done for SNAP (26) and
APACHE (27-29) development. Follow-up to six weeks’ postpartum (or ultimate postnatal hospital discharge, if later) was conducted for both the mothers and their newborns to ensure that there were no readmissions for adverse outcomes.

Data were abstracted directly from the patient medical records onto the customized case report forms, and then into the customized Access® database. Data from all sites were downloaded monthly into a central database, and checked for completeness and to confirm the values of any extreme data points. Random re-abstraction was performed in 5% of cases, and for all cases in which adverse maternal outcomes were suspected or confirmed, to ensure accuracy.

### A3 Statistical plan and methods

#### A3.1 Sample size

An initial sample size of 2000 was thought be necessary for model development, and was made based on the investigation of 20 maternal predictor variables using the following equation:

\[(N \times 10)/I \quad (30-32)\]

where

- \(N\) = the number of predictors being considered (initially this was 20)
- \(10\) = the requirement for a minimum of 10 outcomes per predictor considered for valid multivariable regression modeling
- \(I\) = the incidence of our combined adverse outcome (which in the feasibility study was 10% (4)).
However, at an early stage of this study, the rate of adverse maternal outcomes was noticed to be falling in the participating centres (21), as compared with that seen in the feasibility study (4). In response to this, a decision was made to assess model development in an iterative fashion after the first 200 women had been entered into the database and then regularly thereafter, in order to adjust for sample size according to the observed incidence of adverse maternal outcome and so that consistently non-informative variables (i.e. those with a p-value of >0.2 in univariable analyses against the adverse maternal outcome) could be abandoned and so that the selection of one of two or more variables that were consistently found to be highly correlated with each other could be made. The final decision to close study recruitment was left to the study statistician, YC MacNab. The statistician required that the models be stable for a six month period prior to making the decision to stop, both in terms of the variables included in the models and in the area under the receiver-operator curve (AUC ROC, described below) used to assess the discriminative power of the models. The final sample size calculation was made based on the fact that only 11 informative, available and non-correlated variables were consistently identified and that the incidence of adverse maternal outcome in the study cohort was stabilizing at 9-9.5%, as per the following calculation:

\[ N = \frac{(11 \times 10)}{0.095} = 1157 \]  

Recruitment was left open for a time after reaching this sample size, to permit the identification and recruitment of additional eligible patients as a safeguard against any missing data in individual cases in order to improve the study power. Recruitment was finally closed in September 2007 and the final sample size achieved was 1259.
A3.2 Data sources

All data from the 1259 included cases were entered into the PIERS study database. For each case, the “worst value” (e.g. highest AST or lowest platelet count) for the candidate predictor variables to be evaluated were collated from within the first 48 hours of eligibility. In the event that a variable was unavailable from this epoch, the method of “last observation carried forward” was utilized by which the most recent observation of that variable (assessed within the preceeding 2 weeks for laboratory tests, or within 12 hours for symptoms and signs) was considered current. This method is in keeping with clinical practice. Only data points collected prior to the occurrence of any of the elements of the combined adverse maternal outcome were used in any analyses.

A3.3 Statistical Methods

In the primary analyses conducted for the PIERS model development, the candidate predictor variables collected within the first 48h of eligibility were used to predict the combined adverse maternal outcome occurring within the first 48 hours after eligibility. Again, only the ‘worst value’ for each predictor variable which was collected prior to the occurrence of any of the elements of the combined adverse maternal outcome was used in any analyses. The following analytical steps were followed:

1) Univariable analyses: each independent predictor variable was included in a univariable logistic regression analysis against the combined adverse maternal outcome to evaluate the relationship between the two. Only those variables found to be significantly associated with the combined outcome (p-value <0.05) and that were also available in >80% of cases were further evaluated as described below.
2) **Correlation and co-linearity:** To identify those candidate predictor variables that behave most similarly in the model building, Pearson correlation (for continuous variables) and Chi-square (for categorical variables) tests were performed, as were cluster analyses (33). The cluster method uses a function of correlation to calculate the dissimilarity (or similarity) between objects when forming the clusters, resulting in those variables that behave most similarly clustering together (33).

3) **Multivariable model derivation:** In an effort to derive the most parsimonious model possible, the predictor variables considered in the multivariate analyses were chosen based on their availability (>80% of cases), the significance of their univariable associations with the outcome (p < 0.05), their correlations with other candidate variables (one of one/more variables with colinearity selected), and clinical opinion (for face validity).

The discriminative power (i.e. ability to predict the binary outcome) of each fitted model was assessed using the area under the receiver operating curve (AUC ROC) method of Hanley and McNeil (34) in which the ROC curve reveals the relationship between the true-positive and false-positive ratios over a range of possible cut-points that could define a positive test (19;34;35). The area under the ROC curve would therefore represent the probability of correctly discriminating between “outcome” and “no outcome” (19;34), with an AUC ROC of 1.0 signifying a perfectly discriminative test and 0.5 a non-discriminative test. An AUC ROC of >0.70 is considered the minimum for adequacy. The multivariable model with the highest AUC ROC was considered to be the best fitting model.
The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated based on 4 different cut-points for probability of outcome occurrence (5%, 10%, 20% and 30%). The NPV will identify the proportion of women who did NOT go on to have outcomes after the model had predicted that they wouldn’t, with the assumption that it is more important clinically to be able to be confident in predicting that a woman will NOT have an outcome. With a high NPV a clinician can be reasonably confident that a woman will not have an adverse outcome at the probability predicted.

4) **Calibration:** The Hosmer-Lemeshow (36) test was used to determine the “goodness of fit” (i.e. the deviation between observed and expected rates of adverse outcomes) for the derived models.

5) **Initial validation:** An initial validation to assess the performance of the final, most parsimonious models developed was conducted using a ‘leave-one-out’ cross validation technique, in which a single observation from the original sample was treated as the validation data and the remaining observations as the training data. The training data were then used to fit a multiple regression model and the validation data were used for prediction. This process was repeated so that each observation in the dataset was used once as the validation data.
A4 References


(12) Yamasmit W, Chaithongwongwatthana S, Charoenvidhya D, Uerpairojkit B, Tolosa J. Random urinary protein-to-creatinine ratio for prediction of significant


Appendix B

PIERS Case Report Form
Section A: Admission Information

1. During this pregnancy, has the woman fulfilled the eligibility criteria and been started on the standing orders (or their equivalent) as an outpatient?  
   - No  
   - Yes → If yes, please complete an outpatient package.

2. During this pregnancy was the woman previously admitted to this hospital for pre-eclampsia (suspected or confirmed)?  
   - Unknown  
   - No → If no, please record the admission information for this present (and first) admission below. Then continue to section B, question 2.  
   - Yes → If yes, please record the admission information for all previous admissions to this hospital.  
     - Admission information for the first admission may be recorded below.  
     - Admission information for all subsequent re-admissions (including this present admission) may be recorded on separate "Maternal Re-admission" insert forms.  
     - Please ensure to also record any data available from each and all of these admissions in the following form segments (2--Clinical Assessments and Labs; 3--Maternal Outcomes/Delivery; 4--Neonatal Outcomes.) Then continue to section B, question 2.

First admission (admission #1)  

Date and time of admission:  

20yyyy  mm dd : hh:mm  

Date of discharge:  

20yyyy  mm dd  

(a) Was the patient transferred from another institution?  

   - No  
   - Yes → If yes, what was the date and time of admission at this other institution?  

   20yyyy  mm dd : hh:mm  

*Please ensure to also record data available from this other institution in the following form segments: (2--Clinical Assessments and Labs; 3--Maternal Outcomes/Delivery; 4--Neonatal Outcomes.)

(b) Marital status:  

   - Married or living together  
   - Single  
   - Not specified

(c) Present Pregnancy Weight:  

   - kg  
   - lbs  

(d) At the time of this first admission, does the woman have any of the following in this pregnancy?  

   NOT SPECIFIED  

   NO  

   YES  

   - A new partner?  
   - Gestational diabetes?  
   - A history of smoking (any amount)?  
   - A history of illicit drug use (any amount)?  

(e) Has the woman been put on the standing orders (or their equivalent)?  

   - No  
   - Yes → If yes, please mark all that apply:  

   - antepartum orders  
   - postpartum orders  

   → If yes, what was used:  

   (Please mark ALL that apply)  

   - Cocaine  
   - Crystal methamphetamine  
   - Ecstasy  
   - Other(s)  

Version 1.15
Section B: Identifiers

3. Mother’s ethnicity (choose the most appropriate one):
   - Caucasian
   - South Asian
   - Pacific Islanders/Maori
   - Black
   - 1st Nations
   - Australian Aborigines
   - Not specified
   - East Asian
   - Latino
   - Arabic/Middle Eastern
   - Other

4. Estimated date of delivery (EDD): 2 0 y m d
   Year     Month     Day
   Was the EDD confirmed by ultrasound? ○ No  ○ Yes

5. Number of fetuses: (in current pregnancy; must be ≥ 1)

6. Pre-pregnancy weight: □□□□.□ kg OR □□□□ lbs  ○ Not specified

7. Height: □□□□.□ cm OR □□□□ feet □□ inches  ○ Not specified

8. Pre-pregnancy or booking blood pressure: sBP □□□□
   dBP □□□□
   ○ Not specified

9. Date pre-eclampsia first diagnosed: 2 0 y m d
   Year     Month     Day
   ○ Not diagnosed prior to first admission

10. Gravidity Term Preterm Spontaneous Abortion Therapeutic Abortion Living
    □□ □□ □□ 34^0^0^-36^6^ weeks □□ <10 weeks □□ □□
    □□ <34 weeks □□ ≥ 10 weeks
    □□
    If spontaneous abortions are ≥ 3, were they consecutive?
    ○ No  ○ Yes

11. Parity: □□
    (Number of previous deliveries of fetus at ≥ 20 weeks’ gestation or ≥ 500 g birthweight)
    If parity is ≥ 1 (i.e. one or more previous deliveries), please complete Section C on next page.
    Otherwise skip to Section D.
Section C: Previous adverse pregnancy outcomes

12. Did the woman develop any of the following in previous pregnancies?  
(Please mark answer for each, or if none apply, mark “None”)  
○NONE

<table>
<thead>
<tr>
<th></th>
<th>NOT SPECIFIED</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Gestational hypertension*</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>b) Gestational proteinuria†</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>c) Gestational diabetes</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>d) Other(s)</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
</tbody>
</table>

*Gestational hypertension is defined as dBP > 90mm Hg and/or sBP > 140 mmHg, measured twice > 4 hours apart.

†Proteinuria is defined as > 0.3 g/d or > 2+ dipstick.

Section D: Medical History

13. Did the woman have any of the following, either before this pregnancy or before 20 weeks’ gestation in this pregnancy?  
(Please mark answer for each, or if none apply, mark “None”)  
○NONE

<table>
<thead>
<tr>
<th></th>
<th>NOT SPECIFIED</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Thromboembolism [i.e. DVT/PE or other, but NOT superficial (i.e. thrombosis)]</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
<tr>
<td>b) Cardiovascular disease [i.e. previous MI, angina, or stroke, but NOT mitral valve prolapse (MVP)]</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
<tr>
<td>c) Renal disease</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
<tr>
<td>d) Hypertension</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>e) Pre-gestational diabetes</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>f) Other(s)</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
</tbody>
</table>

Section E: Family History

14. Is there a history of any of the following conditions in first degree relatives on the woman’s side of the family?  
(Please mark answer for each, or if none apply, mark “None”)  
○NONE

<table>
<thead>
<tr>
<th></th>
<th>NOT SPECIFIED</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Pre-eclampsia</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>b) Thromboembolism [i.e. DVT/PE or other, but NOT superficial (i.e. thrombosis)]</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
<tr>
<td>c) Cardiovascular disease [i.e. MI, angina or stroke prior to age 60]</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
<tr>
<td>d) Hypertension</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>e) Diabetes</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>f) Other(s)</td>
<td>○</td>
<td>○</td>
<td>○→If yes, specify:_______________</td>
</tr>
</tbody>
</table>
Section F: Treatment During This Pregnancy

15. During this pregnancy, is the woman receiving (or has she received) any of the following before her first admission?

a) Corticosteroids
   - Unknown  ○ No  ○ Yes → If yes, specify reason for use, which corticosteroids were used and date of first use: (mark ALL that apply)

<table>
<thead>
<tr>
<th>For fetal lung maturity</th>
<th>Year</th>
<th>Month</th>
<th>Day</th>
<th>Before pregnancy</th>
<th>Before pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Betamethasone</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>○ Dexamethasone</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>For H.E.L.L.P. syndrome</th>
<th>Year</th>
<th>Month</th>
<th>Day</th>
<th>Before pregnancy</th>
<th>Before pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Betamethasone</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>○ Dexamethasone</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
</tbody>
</table>

b) Oral antihypertensives
   - Unknown  ○ No  ○ Yes → If yes, specify oral antihypertensive agents used and date of first use: (mark ALL that apply)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year</th>
<th>Month</th>
<th>Day</th>
<th>Before pregnancy</th>
<th>Before pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Labetalol</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>○ Methyldopa</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>○ Nifedipine long acting*</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>○ Nifedipine intermediate acting†</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>○ Beta-blocker other than labetalol</td>
<td>2019</td>
<td>m m</td>
<td>d d</td>
<td>2019</td>
<td>2019</td>
</tr>
<tr>
<td>○ Other</td>
<td>Year</td>
<td>Month</td>
<td>Day</td>
<td>Before pregnancy</td>
<td>Before pregnancy</td>
</tr>
</tbody>
</table>

*Long acting nifedipine = XL or Oros
†Intermediate acting nifedipine = PA or Retard
c) Short-acting antihypertensives for acutely elevated blood pressure

- Unknown
- No
- Yes → If yes, specify short-acting antihypertensive agents used and the date of first use: (mark ALL that apply)

- Parenteral labetalol (intravenous) start date → Y Y M M D D  O before pregnancy
- Parenteral hydralazine (intravenous/intramuscular) start date → Y Y M M D D  O before pregnancy
- Nifedipine capsule start date → Y Y M M D D  O before pregnancy
- Other specify start date → Y Y M M D D  O before pregnancy

d) MgSO₄

- Unknown
- No
- Yes → If yes, specify the date of first use:

- Y Y M M D D  O before pregnancy

e) Aspirin (ASA)

- Unknown
- No
- Yes → If yes, specify the date of first use:

- Y Y M M D D  O before pregnancy

f) Narcotics/Opiates (Includes methadone, but EXCLUDES epidural or spinal narcotics/opiates)

- Unknown
- No
- Yes → If yes, specify the date of first use:

- Y Y M M D D  O before pregnancy

g) Other(s) (EXCLUDES prenatal vitamins, minerals, labour induction therapy, local anaesthetics, antibiotics, anti-anxiety or anti-nausea medications, laxatives and antacids)

- Unknown
- No
- Yes → If yes, specify medication and the date of first use:

- specify start date → Y Y M M D D  O before pregnancy
h) Medications/drugs received as part of participation in other studies/trials (e.g. INTAPP, VIP, CHIPS)
   - Unknown
   - No
   - Yes → If yes, specify the study/trial, the arm the patient is enrolled in, and date of first administration of the treatment:
     - Study/trial name
     - Start date → Year: MM/DD
     - Arm
     - Study/trial name
     - Start date → Year: MM/DD
     - Arm

16. Within the 2 weeks prior to her first admission, did the woman have an ultrasound?
   - Unknown
   - No
   - Yes → If yes, please enter the results from the most recent ultrasound under the “Pre-admission” column heading in the table labelled “Fetal Assessments” (Table 3) located in the following form segment: Segment 2—Clinical Assessments and Labs.
### Clinical Assessments

<table>
<thead>
<tr>
<th>Test date (yyyy/mm/dd)</th>
<th>Location (if transferred)</th>
<th>Pre-admission BP measurement with highest sBP per date</th>
<th>Study site sBP</th>
<th>Study site dBP</th>
<th>Study site highest reading per date</th>
<th>Study site highest dBP per date</th>
<th>Study site highest sBP per date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Other site</th>
<th>Pre-admission BP measurement with highest sBP per date</th>
<th>Study site sBP</th>
<th>Study site dBP</th>
<th>Study site highest reading per date</th>
<th>Study site highest dBP per date</th>
<th>Study site highest sBP per date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
<td>sBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
<td>dBP</td>
</tr>
</tbody>
</table>

| SaO2 (%)                | lowest reading per date   | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |
|                        |                           | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |
|                        |                           | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |

|                        |                           | Trace                                                  | Trace          | Trace         | Trace                            | Trace                         | Trace                           |

| Total fluid input (ml/d)| (if available)            | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |
|                        |                           | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |
|                        |                           | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |

| Total urine output (ml/d)| (if available)            | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |
|                        |                           | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |
|                        |                           | ONS                                                    | ONS            | ONS           | ONS                              | ONS                           | ONS                            |

<table>
<thead>
<tr>
<th>Units of blood or blood products transfused (# of units)</th>
<th>RBCs</th>
<th>RBCs</th>
<th>RBCs</th>
<th>RBCs</th>
<th>RBCs</th>
<th>RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cryo</td>
<td>Cryo</td>
<td>Cryo</td>
<td>Cryo</td>
<td>Cryo</td>
<td>Cryo</td>
</tr>
<tr>
<td></td>
<td>FFP</td>
<td>FFP</td>
<td>FFP</td>
<td>FFP</td>
<td>FFP</td>
<td>FFP</td>
</tr>
<tr>
<td></td>
<td>Platelet</td>
<td>Platelet</td>
<td>Platelet</td>
<td>Platelet</td>
<td>Platelet</td>
<td>Platelet</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason(s) for transfusion (if applicable)</th>
<th>ONS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Eclamptic seizures (#)</th>
<th># of seizures</th>
<th># of seizures</th>
<th># of seizures</th>
<th># of seizures</th>
<th># of seizures</th>
<th># of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary oedema</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe nausea/vomiting</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Frontal headache</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Right upper quadrant pain/epigastric pain</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest pain or dyspnoea</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical impression of maternal condition (as indicated in medical records)</th>
<th>Better</th>
<th>Same</th>
<th>Worse</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Better</td>
<td>Same</td>
<td>Worse</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
### Table 2. Maternal Lab Investigations:

<table>
<thead>
<tr>
<th>Test date (yyyy/mm/dd)</th>
<th>Time 24:00 (24 hr. clock)</th>
<th>Location (if transferred)</th>
<th>Pre-admission (within 2 weeks)</th>
<th>Study site</th>
<th>Study site</th>
<th>Study site</th>
<th>Study site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 / mm / dd</td>
<td>20 / mm / dd</td>
<td>20 / mm / dd</td>
<td>20 / mm / dd</td>
</tr>
<tr>
<td>Hematological:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells WBC (10^9 cells/L)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets (10^9/L)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean platelet volume MPV (FL)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Large platelet forms present?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Coagulation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Chemistry:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (mM)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (µM)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid (µM)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>AST or ASAT (U/L)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ALT or ALAT (U/L)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Unconjugated bilirubin (µM)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Conjugated bilirubin (µM)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total bilirubin (µM)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Random glucose (mM)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2 continued→
### Table 2 (continued). Maternal Lab Investigations:

<table>
<thead>
<tr>
<th>Test date (yyyy/mm/dd)</th>
<th>20yy/mm/dd</th>
<th>20yy/mm/dd</th>
<th>20yy/mm/dd</th>
<th>20yy/mm/dd</th>
<th>20yy/mm/dd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Other site (if transferred)</td>
<td>Pre-admission (within 2 weeks)</td>
<td>Study site</td>
<td>Study site</td>
<td>Study site</td>
</tr>
<tr>
<td>Random urinalysis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a random urinalysis performed?</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
</tr>
<tr>
<td>Random urinary creatinine (mmol/L)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
<tr>
<td>Random urinary protein (g/L)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
<tr>
<td>Protein:creatinine ratio (g/mmol)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
<tr>
<td>24 hour urinalysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a 24 hour urinalysis performed?</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
<td>○Yes ○ No</td>
</tr>
<tr>
<td>Date results reported</td>
<td>20yy/mm/dd</td>
<td>20yy/mm/dd</td>
<td>20yy/mm/dd</td>
<td>20yy/mm/dd</td>
<td>20yy/mm/dd</td>
</tr>
<tr>
<td>Volume (L/d)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
<tr>
<td>[Conc.] of urinary creatinine (mmol/L)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
<tr>
<td>[Conc.] of urinary protein (g/L)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
<tr>
<td>Urinary creatinine excretion (mmol/d)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
<tr>
<td>Urinary protein excretion (g/d)</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
<td>ONS</td>
</tr>
</tbody>
</table>
### Table 3. Fetal Assessments:

Form for:  

<table>
<thead>
<tr>
<th>Test date (yyyy/mm/dd)</th>
<th>Location</th>
<th>Other site (if transferred)</th>
<th>Pre-admission (within 2 weeks)</th>
<th>Study site</th>
<th>Study site</th>
<th>Study site</th>
<th>Study site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was an ultrasound performed?</td>
<td>Yes  No  Yes  No  Yes  No  Yes  No  Yes  No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 24:00 (24 hr. clock)</td>
<td>24 : 00 24 : 00 24 : 00 24 : 00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amniotic fluid index (mm)</td>
<td>mm  mm  mm  mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deepest amniotic fluid pocket (mm)</td>
<td>mm  mm  mm  mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated fetal weight (grams)</td>
<td>g  g  g  g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal circumference (mm)</td>
<td>mm  mm  mm  mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biophysical profile (score out of 8)</td>
<td>8  8  8  8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbilical artery Doppler Diastolic flow</td>
<td>Present  Absent  Reversed  Present  Absent  Reversed  Present  Absent  Reversed  Present  Absent  Reversed  Present  Absent  Reversed  Present  Absent  Reversed  Present  Absent  Reversed  Present  Absent  Reversed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery Doppler Pulsatility index (PI) or Resistance index (RI)</td>
<td>OPI  ONS  OPI  ONS  OPI  ONS  OPI  ONS  OPI  ONS  OPI  ONS  OPI  ONS  OPI  ONS  OPI  ONS  OPI  ONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate trace:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a CTG or NST performed?</td>
<td>Yes  No  Yes  No  Yes  No  Yes  No  Yes  No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 24:00 (24 hr. clock)</td>
<td>24 : 00 24 : 00 24 : 00 24 : 00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate trace</td>
<td>Rating visual</td>
<td>Normal  Suspicious  Pathological  Normal  Suspicious  Pathological  Normal  Suspicious  Pathological  Normal  Suspicious  Pathological  Normal  Suspicious  Pathological  Normal  Suspicious  Pathological  Normal  Suspicious  Pathological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computerized or visual</td>
<td>Short term variability</td>
<td>Computerized (msec)</td>
<td>ONS  ONS  ONS  ONS  ONS  ONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical impression:</td>
<td>Clinical impression of fetal condition (as indicated in medical records)</td>
<td>Better  Same  Worse  Unclear  Better  Same  Worse  Unclear  Better  Same  Worse  Unclear  Better  Same  Worse  Unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section A: Events during course of pregnancy

1. Between the time of her first admission (for suspected/confirmed pre-eclampsia), and ultimate hospital discharge, did the woman receive any of the following for the first time in this pregnancy?

   a) Corticosteroids
      - Unknown  ○ No  ○ Yes → If yes, specify reason for use, which corticosteroids were used and date of first use: (Please mark ALL that apply)

      - ○ for fetal lung maturity
        - Betamethasone  start date → 20
        - Dexamethasone  start date → 20

      - ○ for H.E.L.L.P. syndrome
        - Betamethasone  start date → 20
        - Dexamethasone  start date → 20

   b) Oral antihypertensives
      - Unknown  ○ No  ○ Yes → If yes, specify oral antihypertensive agents used and date of first use: (Please mark ALL that apply)

      - ○ Labetalol  start date → 20
      - Methyldopa  start date → 20
      - Nifedipine long acting*  start date → 20
      - Nifedipine intermediate acting†  start date → 20
      - Beta-blocker other than labetalol  specify __________________________

      ○ Other  specify __________________________  start date → 20
      ○ Other  specify __________________________  start date → 20

*Long acting nifedipine = XL or Oros
†Intermediate acting nifedipine = PA or Retard

Question 1 continued→
c) Short-acting antihypertensives for acutely elevated blood pressure
   - Unknown
   - No
   - Yes → If yes, specify short-acting antihypertensive agents used and date of first use: (Please mark ALL that apply)

   - Parenteral labetalol (intravenous)
     - start date → 2020
   - Parenteral hydralazine (intravenous/intramuscular)
     - start date → 2020
   - Nifedipine capsule
     - start date → 2020
   - Other ________________
     - start date → 2020

   d) MgSO4
      - Unknown
      - No
      - Yes → If yes, specify date of first use:
        - Year 2020
        - Month
        - Day

   e) Aspirin (ASA)
      - Unknown
      - No
      - Yes → If yes, specify date of first use:
        - Year 2020
        - Month
        - Day

   f) Narcotics/Opiates (Includes methadone, but EXCLUDES epidural or spinal narcotics/opiates)
      - Unknown
      - No
      - Yes → If yes, specify date of first use:
        - Year 2020
        - Month
        - Day

   g) Other(s) (EXCLUDES prenatal vitamins, minerals, labour induction therapy, local anaesthetics, antibiotics, anti-anxiety or anti-nausea medications, laxatives and antacids)
      - Unknown
      - No
      - Yes → If yes, specify medication and date of first use:
        - Year 2020
        - Month
        - Day
        - specify

Question 1 continued→
h) Medications/drugs received as part of participation in other studies/trials (e.g. INTAPP, VIP, CHIPS)
   ○ Unknown  ○ No  ○ Yes → If yes, specify the study/trial, the arm the patient is enrolled in, and date of first administration of the treatment:

   ○  
   study/trial name
   start date → 
   Year  Month  Day  

   arm

   ○  
   study/trial name
   start date → 
   Year  Month  Day  

   arm

Section B: Adverse maternal outcomes

2. Did any of the following serious maternal complications develop between first admission and ultimate hospital discharge?

   a) Mortality (maternal)  NO  YES
   Date of death
   ○  ○ if yes → 
   Year  Month  Day  

   Hepatic:
   b) Hepatic dysfunction† (INR greater than 1.2 in the absence of disseminated intravascular coagulation (DIC)* or treatment with Warfarin (Coumadin®).
   If DIC* is present, or if the patient is receiving Warfarin (Coumadin®), then hepatic dysfunction is defined as mixed hyperbilirubinaemia (> 17 µM), or hypoglycaemia (< 2.5 mM) in the absence of insulin.)
   *DIC is defined on page 32 of the Working Protocol.
   †This definition amended November 20, 2006

   ○  ○ if yes → 
   Year  Month  Day  

   c) Hepatic haematoma/rupture
   (Defined by the presence of blood collection under the hepatic capsule as confirmed by ultrasound or at laparotomy.)

   ○  ○ if yes → 
   Year  Month  Day  

   Question 2 continued→
Central Nervous System:

**d)** Glasgow coma score < 13 *(GCS is a scale that assesses the degree of coma in patients with craniocerebral injuries and also assesses brain function, brain damage, and patient progress. It is a composite measure that combines separate scores for the patient's eye opening, verbal, and motor responses. Please refer to the GCS scoring system located on page 32 of the working protocol for details.)*

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- if yes → 20yy mm dd

**e)** Stroke *(Acute neurological event with deficits lasting greater than 48 hours)*

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- if yes → 20yy mm dd

**f)** Cortical blindness *(Loss of visual acuity in the presence of intact pupillary response to light)*

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- if yes → 20yy mm dd

**g)** Other severe neurological events *(Examples: RIND, retinal detachment)*

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- if yes → specify event, date of first occurrence and number of episodes

**CNS investigations:** *(applies to all CNS outcomes listed in items ‘d’ through ‘g’ above)*

Please indicate investigation(s) conducted and record any findings below:

**Investigation:**
- MR (magnetic resonance)
- CT (computerized tomography)

**Findings:**
- 
- 
- 
- 
- 
- 
- 
- 
- 
- 

Version 1.15
Renal:

h) Dialysis *(May include haemodialysis or peritoneal dialysis.)*

<table>
<thead>
<tr>
<th></th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>20 y y m m d d</td>
<td></td>
</tr>
</tbody>
</table>

Cardiovascular:

i) Positive inotropic support required *(The use of vasopressors to maintain a systolic blood pressure of >90 mmHg or a mean arterial pressure >70mmHg.)*

<table>
<thead>
<tr>
<th></th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>20 y y m m d d</td>
<td></td>
</tr>
</tbody>
</table>

j) Infusion of a third injectable antihypertensive *(nitroprusside, nitroglycerine/glyceryl trinitrate (NTG/GTN), and/or diazoxide)* *(Indication that patient has received infusion of a 3rd injectable antihypertensive because of uncontrollable hypertension.)*

<table>
<thead>
<tr>
<th></th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>20 y y m m d d</td>
<td></td>
</tr>
</tbody>
</table>

k) Myocardial ischaemia/infarction

*(Criteria for myocardial ischaemia: ECG changes (ST segment elevation or depression) without enzyme changes.)*

**Criteria for established myocardial infarction:** Any one of the following criteria satisfies the diagnosis for established MI: 1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed. 2) Pathological findings of a healed or healing MI.

**Criteria for acute, evolving or recent myocardial infarction:** Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI: 1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischaemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischaemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty). 2) Pathological findings of an acute MI.

<table>
<thead>
<tr>
<th></th>
<th>Date of first occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>20 y y m m d d</td>
<td></td>
</tr>
</tbody>
</table>

Respiratory:

l) Require ≥ 50% O₂ for > 1hour

<table>
<thead>
<tr>
<th></th>
<th>Date of First Occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>20 y y m m d d</td>
<td></td>
</tr>
</tbody>
</table>

m) Intubation *(vent, EIT, CPAP) other than for Caesarean section*

<table>
<thead>
<tr>
<th></th>
<th>Date of First Occurrence</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>20 y y m m d d</td>
<td></td>
</tr>
</tbody>
</table>
Other adverse maternal events:

NO  YES

☐  ☐ if yes → specify event, date of first occurrence and number of episodes

Date of first occurrence

<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
<th>Day</th>
<th># of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>y</td>
<td>m</td>
<td>d</td>
</tr>
</tbody>
</table>

Section C: Delivery

3. Please indicate reasons for delivery by marking the appropriate boxes:

Maternal (please mark ALL that apply):

☐ Severe uncontrolled hypertension
  (as indicated in medical records, OR sBP ≥ 170mmHg, OR dBP ≥ 110mmHg)

☐ Gestational hypertension (sBP ≥ 140 mmHg or dBP ≥ 90mmHg) at or near term (≥ 36 weeks)

☐ Blood pressure control perceived to be poor (as indicated in medical records)

☐ Heavy proteinuria (≥ 3 g/d or ≥ 4+ dipstick)

☐ Eclampsia (occurrence of 1 or more eclamptic seizures)

☐ Platelet count < 100 x 10^9/L

☐ AST or ALT > 2 times upper limit of normal with epigastric pain or RUQ pain

☐ Pulmonary oedema (clinically diagnosed with one of: oxygen saturation <95% and/or radiological evidence)

☐ Compromised renal function (creatinine above the upper limit of the normal non-pregnancy range used in the hospital, and/or oliguria (<30 ml/hr) or anuria (no urine output) for at least 2 hrs.

☐ Persistent severe headache or visual changes (as indicated in medical records)

☐ Spontaneous labour → if yes, please specify date and time of onset of first stage of labour:

  200:00

☐ Other (please specify)

Fetal (Please mark ALL that apply):

☐ Non-reassuring fetal heart rate (FHR) tracing

☐ BPP ≤ 6

☐ Reduced amniotic fluid volume/oligohydramnios (as indicated in medical records)

☐ Ultrasonographic estimate of fetal weight ≤ 5th percentile

☐ Reversed end-diastolic flow in umbilical artery by doppler velocimetry

☐ Absent end-diastolic flow in umbilical artery by doppler velocimetry

☐ Other (please specify)
4. Was labour induced?
   ○ No    ○ Yes

5. What type of analgesia or anaesthesia was administered? *(Please mark ALL that apply)*
   ○ None
   ○ Narcotics (iv/im)
   ○ General anaesthesia
   ○ Regional anaesthesia—specify type of regional anaesthesia used:
     ○ Spinal
       ○ Epidural
       ○ Combined spinal epidural (CSE)
     ○ Nitrous oxide (N₂O₂)
     ○ Other __________________________

6. Were there any major complications of analgesia or anaesthesia?
   ○ No    ○ Yes if yes—specify complication: *(Please mark ALL that apply)*
     ○ Difficult or failed intubation
     ○ Epidural or spinal haematoma
     ○ Other(s) __________________________

7. Was there evidence of placental abruption at time of delivery?
   ○ No    ○ Yes if yes—specify date of first occurrence and total number of episodes that occurred
   *(as indicated in medical records):*
   
<table>
<thead>
<tr>
<th>2 0</th>
<th>y y</th>
<th>m m</th>
<th>d d</th>
<th># of episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>year</td>
<td>month</td>
<td>day</td>
<td></td>
</tr>
</tbody>
</table>

   If yes—specify the primary manner by which placental abruption was diagnosed
   choose one: ○ Clinical    ○ Ultrasound confirmed    ○ Delivery confirmed

   If yes—was it clinically significant? ○ No    ○ Yes
8. For day of delivery (i.e. between 12 a.m. (24:00) and 11:59 p.m. (23:59) on the day of delivery), record:
   a) the blood pressure measurements containing the highest systolic blood pressures recorded
      before (antepartum), during (intrapartum), and after (postpartum) parturition
      AND
   b) the blood pressure measurements containing the highest diastolic blood pressures recorded
      before (antepartum), during (intrapartum), and after (postpartum) parturition.

   **Highest sBPs:**
   - **Antepartum**
     - sBP
     - dBP
     - ☐ not applicable
   - **Intrapartum**
     - sBP
     - dBP
     - ☐ not applicable
   - **Postpartum**
     - sBP
     - dBP
     - ☐ not applicable

   **Highest dBPs:**
   - **Antepartum**
     - sBP
     - dBP
     - ☐ not applicable
   - **Intrapartum**
     - sBP
     - dBP
     - ☐ not applicable
   - **Postpartum**
     - sBP
     - dBP
     - ☐ not applicable

---

**Section D: Events after delivery**

9. Has the woman been put on the post-partum standing orders (or their equivalent)?
   ☐ No  ☐ Yes

10. To where was the woman discharged?

   a) **Home**  ☐ No  ☐ Yes → If yes, indicate date of ultimate discharge home after delivery
       (or date of death if maternal death occurred prior to discharge):

       ![Discharge Date](image)

   b) **Another institution**  ☐ No  ☐ Yes → If yes, indicate the name of the institution to which she
       was transferred and date of transfer:

       ![Transferred Institution](image)

       → If yes, indicate the date of the woman’s final discharge
       HOME from this other institution (or date of death if
       maternal death occurred prior to discharge):

       ![Final Discharge](image)
**NEONATAL OUTCOMES**

**SEGMENT 4**

**Form for:**
- Singleton or Baby A
- Baby B
- Baby C
- Baby D
- Baby E

1. **What was the mode of delivery?**
   *(please choose one)*
   - Spontaneous vaginal
   - Operative vaginal
   - Caesarean section→
     - laboured
     - non-laboured

2. **Baby’s date and time of birth:**
   - Year
   - Month
   - Day
   - 24 hour clock
   - 2 0  y  y   m m  d  d  2 4 : 0 0

3. **Gender:**
   - Male
   - Female
   - Indeterminate

4. **Status of the baby at birth:**
   - Alive
   - Stillborn→ if stillborn, **what was the primary cause of death?** *(mark ALL that apply)*
     - a. Congenital anomaly
       - No
       - Yes → if yes, specify_______________
     - b. Other
       - No
       - Yes → if yes, specify_______________
     → if stillborn, **was there an autopsy?**
     - No
     - Yes→ if yes, please attach a copy of the autopsy report

5. **Apgar score at 5 minutes:**
   - Not recorded

6. **Birthweight:**
   - grams
   - Not recorded

If baby stillborn, then data collection is now complete. Thank you. Otherwise, please proceed.

7. **Was cord taken for blood gases?**
   - Not recorded
   - No
   - Yes → if yes, indicate vessel blood sample(s) taken from and any results:
     *(report numerical value or mark “not done”)*
     - Arterial
       - pH
         - .
         - pH not done
       - base excess
         - +/-
         - mmol/L
         - base excess not done
     - Venous
       - pH
         - .
         - pH not done
       - base excess
         - +/-
         - mmol/L
         - base excess not done
     - Unclear
       - pH
         - .
         - pH not done
       - base excess
         - +/-
         - mmol/L
         - base excess not done
8. Did the baby have respiratory distress after the initial resuscitation/stabilisation?
   - No
   - Yes → if yes, what was the cause? (Please mark ALL that apply)
     - Respiratory distress syndrome
     - Meconium aspiration syndrome
     - Pneumonia
     - Pneumothorax/pneumomediastinum
     - Transient tachypnoea of the newborn
     - Other ____________________________
     → specify

9. Did the baby receive supplemental oxygen after the initial resuscitation/stabilisation?
   - No
   - Yes → if yes, indicate date and time oxygen first started:
     20__-___-______ 24:00
     → if yes, indicate date and time oxygen finally stopped, or the date of discharge if sent home on oxygen:
     20__-___-______ 24:00

10. Did the baby receive intubation and ventilation via endotracheal tube after the initial resuscitation/stabilisation?
    - No
    - Yes → if yes, indicate date and time endotracheal ventilation first started:
      20__-___-______ 24:00
      → if yes, indicate date and time endotracheal ventilation finally stopped:
      20__-___-______ 24:00

11. Did the baby receive any other ventilatory support without intubation after the initial resuscitation/stabilisation? (nasopharyngeal, nasal cannula, mask, CPAP)
    - No
    - Yes → if yes, indicate date and time other support first started:
      20__-___-______ 24:00
      → if yes, indicate date and time other support finally stopped:
      20__-___-______ 24:00

12. Did the baby receive surfactant?
    - No
    - Yes → if yes, indicate date and time of first dose:
      20__-___-______ 24:00
      → if yes, was the surfactant given for prophylaxis? No

13. Did the baby have any chest X-rays?
   ☐ No ☐ Yes → if yes, was there an abnormal X-ray?
      ☐ No ☐ Yes → if yes, was it compatible with: (Please mark ALL that apply)
      a. RDS (Respiratory Distress Syndrome) ☐ No ☐ Yes → if yes, date of X-ray:
         2 0 y y m m d d
      b. BPD (Bronchopulmonary Dysplasia) ☐ No ☐ Yes → if yes, date of X-ray:
         2 0 y y m m d d
      c. Other (specify) ____________________ ☐ No ☐ Yes → if yes, date of X-ray:
         2 0 y y m m d d

14. Did the baby have necrotising enterocolitis (NEC)?
   ☐ No ☐ Yes → if yes, did the baby have: (Please mark ALL that apply)
   a. Perforation of the intestine ☐ No ☐ Yes
   b. Pneumatosis intestinalis ☐ No ☐ Yes
   c. Air in the portal vein ☐ No ☐ Yes

   If any yes, was this confirmed by: (Please mark ALL that apply)
   i. Surgery ☐ No ☐ Yes
   ii. X-ray ☐ No ☐ Yes
   iii. Post-mortem exam ☐ No ☐ Yes

15. Did the baby have head ultrasounds prior to discharge?
   ☐ No ☐ Yes
      → if yes, did the baby have intraventricular haemorrhage (IVH)?
         ☐ No ☐ Yes → if yes, what was the most severe grade? □ (1-4)
      → if yes, did the baby have cystic periventricular leukomalacia (PVL)?
         (exclude sub-ependymal and choroid plexus cysts)
         ☐ No ☐ Yes

16. Did the baby have an ophthalmologic exam to check for retinopathy of prematurity (ROP)?
   ☐ No ☐ Yes → if yes, did the baby have ROP?
      ☐ No ☐ Yes → if yes, what was the most severe stage in either eye? □ (1-5)
17. Was the baby admitted to a level III (intensive care) nursery? (e.g. NICU, SCN)
   ○ No  ○ Yes → if yes, indicate date and time of admission and discharge from level III nursery:

   Date and time of admission: 2 0 y y m m d d 2 4 0 0
   year month day 24 hour clock

   Date and time of discharge: 2 0 y y m m d d 2 4 0 0
   year month day 24 hour clock

18. Did the baby die prior to discharge from hospital?
   ○ No  ○ Yes → if yes, indicate date and time of death:

   2 0 y y m m d d 2 4 0 0
   year month day 24 hour clock

   → if yes, what was the primary cause of death: (Please mark ALL that apply)
   a. Congenital anomalies ○ No ○ Yes
   b. Multiple cardiac anomalies ○ No ○ Yes
   c. Adequate ventilation not achieved ○ No ○ Yes
   d. Complications of preterm birth ○ No ○ Yes
   e. Other ______________________ ○ No ○ Yes

   → if yes, was there an autopsy?
   ○ No  ○ Yes → if yes, please attach a copy of the autopsy report

19. To where was the baby discharged?
   a) Home ○ No  ○ Yes → If yes, indicate date and time of discharge home:

   2 0 y y m m d d 2 4 0 0
   Year Month Day 24 hour clock

   b) Another institution ○ No  ○ Yes → If yes, indicate the name of the institution to which baby was transferred and date and time of transfer:

   Name of institution 2 0 y y m m d d 2 4 0 0
   Year Month Day 24 hour clock

   → If yes, indicate the date of baby’s final discharge HOME from this other institution (or date of death if infant death occurred prior to discharge):

   2 0 y y m m d d ○ Not known
MATERNAL—ADVERSE OUTCOME REPORT

To be completed for EACH adverse maternal outcome that occurs.
(If a patient has fulfilled the criteria for more than 1 adverse outcome, then a separate form must be filled out for each outcome that occurred.)

1. Please specify the adverse maternal outcome which occurred and the DATE and TIME that it first took place and/or was first reported:
   (a) Outcome: ____________________________________________________________
   (b) Date and time adverse outcome first occurred and/or was first reported:

   Date                     Time
   ______________________   __________________________
   2 0 y y m m d d       2 4 : 0 0
   Year         Month        Day    24 hour clock

2. Has the patient fulfilled the PIERS eligibility criteria PRIOR to developing this adverse maternal outcome?
   O Yes—if “yes” please continue to Question 3 and the rest of the form
   O No—if “no”, this patient is Not Eligible as she has developed the outcome prior to fulfilling the eligibility criteria.

3. Did this adverse outcome occur WITHIN the FIRST 48 hours after the patient had fulfilled the ELIGIBILITY CRITERIA?
   O Yes  →  please complete Section A below.
   O No →  please complete Section B below.
Section A: To be completed if the adverse outcome occurred WITHIN the FIRST 48 hours after the patient fulfilled the eligibility criteria.

Please fill in the table below with the most abnormal clinical assessments recorded BETWEEN the time of eligibility and the occurrence of the adverse outcome (i.e. Enter ONLY those assessments recorded BEFORE the adverse outcome took place).

For example: If the patient fulfilled eligibility criteria on 1-January-2006 @ 07:00 and developed the adverse outcome on 2-January-2006 @ 10:30, then record the most abnormal values collected between 07:00 on 1-Jan-06 and 10:30 on 2-Jan-06.

For each data variable enter the most abnormal value (specified in italics) that was recorded after eligibility was fulfilled and prior to outcome occurrence:

<table>
<thead>
<tr>
<th>Clinical Assessments Recorded Prior to Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>sBP (mmHg)</td>
</tr>
<tr>
<td>BP measurement with highest sBP</td>
</tr>
<tr>
<td>dBp</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
</tr>
<tr>
<td>BP measurement with highest dBP</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
</tr>
<tr>
<td>lowest reading</td>
</tr>
<tr>
<td>Dipstick protein</td>
</tr>
<tr>
<td>highest reading</td>
</tr>
<tr>
<td>Total fluid input (ml/d)</td>
</tr>
<tr>
<td>(if available)</td>
</tr>
<tr>
<td>Total urine output (ml/d)</td>
</tr>
<tr>
<td>(if available)</td>
</tr>
<tr>
<td>Adverse Conditions:</td>
</tr>
<tr>
<td>Severe nausea/vomiting</td>
</tr>
<tr>
<td>Frontal headache</td>
</tr>
<tr>
<td>Visual disturbances</td>
</tr>
<tr>
<td>Right upper quadrant pain/epigastric pain</td>
</tr>
<tr>
<td>Chest pain or dyspnoea</td>
</tr>
</tbody>
</table>

Version 1.15
Section B: To be completed if the adverse outcome occurred ANYTIME BEYOND the first 48 hours of the patient fulfilling the eligibility criteria.

Please fill in the table below with the clinical assessments recorded PRIOR to the occurrence of the adverse outcome on the same calendar date.

For example: If the patient fulfilled eligibility criteria on 1-January-2006 @ 07:00 and developed the adverse outcome on 5-January-2006 @ 14:00, then record the most abnormal values collected between 24:00 (midnight) and 14:00 on 5-Jan-06.

For each data variable enter the most abnormal value (specified in italics) that was recorded after midnight (12 a.m.) and prior to outcome occurrence (on the same calendar date):

<table>
<thead>
<tr>
<th>Clinical Assessments Recorded Prior to Outcome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>sBP (mmHg) BP measurement with highest sBP</td>
<td></td>
</tr>
<tr>
<td>dBP (mmHg) BP measurement with highest dBP</td>
<td></td>
</tr>
<tr>
<td>SaO₂ (%) lowest reading</td>
<td></td>
</tr>
<tr>
<td>Dipstick protein highest reading</td>
<td>Neg.</td>
</tr>
<tr>
<td></td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fluid input (ml/d) (if available)</td>
<td></td>
</tr>
<tr>
<td>Total urine output (ml/d) (if available)</td>
<td></td>
</tr>
<tr>
<td>Adverse Conditions:</td>
<td></td>
</tr>
<tr>
<td>Severe nausea/vomiting</td>
<td>Yes</td>
</tr>
<tr>
<td>Frontal headache</td>
<td>Yes</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>Yes</td>
</tr>
<tr>
<td>Right upper quadrant pain/epigastric pain</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest pain or dyspnoea</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Version 1.15
Appendix C

UBC Clinical Research Ethics Board Certificates of Approval
Certificate of Expedited Approval

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR</th>
<th>DEPARTMENT</th>
<th>NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Dadelszen, P</td>
<td>Obstetrics/Gynaecology</td>
<td>C03-0137</td>
</tr>
</tbody>
</table>

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Children's & Women's Health Ctr

CO-INVESTIGATORS:
Douglas, Joanne, Anaesthesia; Lee, Shoo, Paediatrics; Magee, Laura, Medicine

SPONSORING AGENCIES
Unfunded Research

TITLE:
Gestational Hypertension and/or Gestational Proteinuria Chart Audit and Review

APPROVAL DATE
MAR 05 2003

TERM (YEARS) DOCUMENTS INCLUDED IN THIS APPROVAL:
1

- Protocol dated 27 February 2003; Physicians' Orders sheet (orders for gestational hypertension and/or gestational proteinuria);
- Postpartum Physicians' Orders; Data Collection worksheet dated February 2003;

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The documentation included for the above-named project has been reviewed by the Chair of the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.

The CREB approval for this study expires one year from the approval date.

Approval of the Clinical Research Ethics Board by one of:
- Dr. P. Loewen, Chair
- Dr. A. Gagnon, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the experimental procedures.
Certificate of Expedited Approval: Renewal  
Clinical Research Ethics Board Official Notification

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR</th>
<th>DEPARTMENT</th>
<th>NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Dadelszen, P</td>
<td>Obstetrics/Gynaecology</td>
<td>C03-0137</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children's &amp; Women's Health Centre</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CO-INVESTIGATORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douglas, Joanne, Anaesthesia; Lee, Shoo, Paediatrics; Magee, Laura, Medicine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPONSORING AGENCIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfunded Research</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TITLE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Hypertension and/or Gestational Proteinuria Chart Audit and Review</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APPROVAL RENEWAL DATE</th>
<th>TERM (YEARS)</th>
<th>AMENDMENT</th>
<th>AMENDMENT APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar 16 2004</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CERTIFICATION:
in respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of the this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

The CREB approval for renewal of this study expires one year from the date of renewal.

__________________________
Approval of the Clinical Research Ethics Board by one of:

Dr. P. Loewen, Chair
Dr. Alain Gagnon, Associate Chair
Dr. James McCormack, Associate Chair
Certificate of Expedited Approval: Amendment
Clinical Research Ethics Board Official Notification

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Von Dadelszen, P</th>
<th>Department</th>
<th>Obstetrics/Gynaecology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution(s) Where Research Will Be Carried Out</td>
<td>Children's &amp; Women's Health Centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-Investigators:</td>
<td>Douglas, Joanne, Anaesthesia; Lee, Shoo, Paediatrics; Magee, Laura, Medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponsoring Agencies:</td>
<td>Canadian Institutes of Health Research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title:</td>
<td>PIERS (Pre eclampsia Integrated Estimate of RiSk) model: Predicting Adverse Maternal Outcomes in Pre-Eclampsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval Date (mm/dd/yyyy)</td>
<td>03-03-05</td>
<td>Term (Years)</td>
<td>1</td>
</tr>
<tr>
<td>Amendment:</td>
<td>Title</td>
<td>Amendment Approved:</td>
<td>April 2 2004</td>
</tr>
</tbody>
</table>

Certification:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of the this Research Ethics Board have been documented in writing.

The amendment(s) for the above-named project has been reviewed by the Chair of the University of British Columbia Clinical Research Ethics Board and the accompanying documentation was found to be acceptable on ethical grounds for research involving human subjects.

The CREB approval period for this amendment expires on the one year anniversary date of the CREB approval for the entire study.

Approval of the Clinical Research Ethics Board by one of:
Dr. P. Loewen, Chair
Dr. A. Gagnon, Associate Chair
Dr. J. McCormack, Associate Chair
The University of British Columbia  
Office of Research Services,  
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

# Certificate of Expedited Approval: Renewal

**Clinical Research Ethics Board Official Notification**

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR</th>
<th>DEPARTMENT</th>
<th>NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Dadelszen, P</td>
<td>Obstetrics/Gynaecology</td>
<td>C03-0137</td>
</tr>
</tbody>
</table>

**Institutions Where Research Will Be Carried Out**

Children's & Women's Health Centre

**Co-investigators**

Douglas, Joanne, Anaesthesia; Lee, Shoo, Paediatrics; Magee, Laura, Medicine

**Sponsoring Agencies**

Canadian Institutes of Health Research

**Title:**

PIERS (Pre-Eclampsia Integrated Estimate of Risk) Model: Predicting Adverse Maternal Outcomes in Pre-Eclampsia

**Approval Renewal Date**

19 January 2005

**Term (Years)**

1

**Amendment**

N/A

**Amendment Approved**

N/A

**Certification:**

In respect of clinical trials:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

The CREB approval for renewal of this study expires one year from the date of renewal.

---

*Approval of the Clinical Research Ethics Board by one of:*

Dr. P. Loewen, Chair  
Dr. Alain Gagnon, Associate Chair  
Dr. James McCormack, Associate Chair  

---

179
Certificate of Expedited Approval: Renewal
Clinical Research Ethics Board Official Notification

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR</th>
<th>DEPARTMENT</th>
<th>NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Dadelszen, P.</td>
<td>Obstetrics/Gynaecology</td>
<td>C03-0137</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children's &amp; Women's Health Centre</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CO-INVESTIGATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douglas, Joanne, Anaesthesia; Lee, Shoo Kim, Paediatrics; Magee, Laura, Medicine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPONSORING AGENCIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Institutes of Health Research</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIERs (Pre-Eclampsia Integrated Estimate of Risk) Model: Predicting Adverse Maternal Outcomes in Pre-Eclampsia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APPROVAL RENEWAL DATE</th>
<th>TERM (YEARS)</th>
<th>AMENEMENT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 January 2006</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERTIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>In respect of clinical trials:</td>
</tr>
<tr>
<td>1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.</td>
</tr>
<tr>
<td>2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.</td>
</tr>
<tr>
<td>3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.</td>
</tr>
</tbody>
</table>

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

The CREB approval for renewal of this study expires one year from the date of renewal.

Approval of the Clinical Research Ethics Board by one of:
Dr. Gail Bellward, Chair
Dr. James McCormack, Associate Chair
ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

PRINCIPAL INVESTIGATOR:  
Peter Von Dadelszen

DEPARTMENT:  
UBC/Medicine, Faculty of Obstetrics & Gynaecology/Maternal Fetal Medicine

UBC CREB NUMBER:  
H03-70137

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

<table>
<thead>
<tr>
<th>Institution</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children's and Women's Health Centre of BC (incl. Sunny Hill)</td>
<td>Children's and Women's Health Centre of BC (incl. Sunny Hill)</td>
</tr>
</tbody>
</table>

Other locations where the research will be conducted:  
N/A

CO-INVESTIGATOR(S):  
Shoo K. Lee  
Laura A. Magee  
M. Joanne Douglas

SPONSORING AGENCIES:  
Canadian Institutes of Health Research - "PIERS (Pre-Eclampsia Integrated Estimate of Risk) Model: Predicting Adverse Maternal Outcomes in Pre-Eclampsia"  
Unfunded Research - "Gestational Hypertension and/or Gestational Proteinuria Chart Audit and Review"

PROJECT TITLE:  
PIERS (Pre-Eclampsia Integrated Estimate of Risk) Model: Predicting Adverse Maternal Outcomes in Pre-Eclampsia

EXPIRY DATE OF THIS APPROVAL:  
January 16, 2008

APPROVAL DATE:  
January 16, 2007

CERTIFICATION:  
In respect of clinical trials:  
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.  
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.  
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and the informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by one of:

Dr. James McCormack, Associate Chair

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

PRINCIPAL INVESTIGATOR:
Peter Von Dadelszen

DEPARTMENT:
UBC/Medicine, Faculty of Obstetrics & Gynaecology/Maternal Health Medicine

UBC CREB NUMBER:
H03-70137

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

<table>
<thead>
<tr>
<th>Institution</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children's and Women's Health Centre of BC (incl. Sunny Hill)</td>
<td>Children's and Women's Health Centre of BC (incl. Sunny Hill)</td>
</tr>
</tbody>
</table>

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Shoo K. Lee
Laura A. Magee
M. Joanne Douglas

SPONSORING AGENCIES:
Canadian Institutes of Health Research (CIHR) - *PIERS (Pre-Eclampsia Integrated Estimate of Risk) Model: Predicting Adverse Maternal Outcomes in Pre-Eclampsia*
Child & Family Research Institute - *PIERS (Pre-eclampsia Integrated Estimate of Risk for mothers): validation across conditions and clinical settings*
Unfunded Research - "Gestational Hypertension and/or Gestational Proteinuria Chart Audit and Review"

PROJECT TITLE:
PIERS (Pre-Eclampsia Integrated Estimate of Risk) Model: Predicting Adverse Maternal Outcomes in Pre-Eclampsia

Please add the following additional title*
PIERS (Pre-eclampsia Integrated Estimate of Risk for mothers): validation across conditions and clinical settings

EXPIRY DATE OF THIS APPROVAL: February 1, 2009

APPROVAL DATE: February 1, 2008

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by:

Dr. James McCormack, Associate Chair