Institution: University of Exeter		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Preventing preeclampsia and preterm births through more effective risk prediction and treatment		
Period when the underpinning research was undertaken: 2014 to present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Professor Dave Wright	Professor of Medical Statistics	2014 to present
Period when the claimed impact occurred: 2016 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Preeclampsia is a potentially serious condition experienced by between 3% and 6% of pregnant women. It is characterised by high blood pressure (associated possible organ damage), higher risks of preterm birth, stillbirth and maternal death. Research designed and conducted by Professor Wright has developed algorithms that combine the use of biomarkers and maternal factors at 1st trimester screening to identify women at high risk of preterm preeclampsia. Use of these algorithms has been adopted widely by obstetricians and gynaecologists in the UK and internationally, with an estimated **9.4 million 1st trimester screens (1.3%) using the algorithm** since 2016. In addition, a clinical trial conducted by Professor Wright has demonstrated that low-dose aspirin can reduce the risk of preeclampsia, preterm birth and the related costs associated with neonatal intensive care (estimated **49,000 cases of preeclampsia prevented** by the end of 2020, with global healthcare **savings of about $3.2 billion**). This cost-effective treatment has also been rapidly **adopted in international clinical guidelines** for obstetric care.

2. Underpinning research (indicative maximum 500 words)

Professor Dave Wright is a medical statistician who has developed various analytical methods for creating statistical algorithms that allow more accurate antenatal prediction of conditions and birth defects (e.g. Down's Syndrome). Since joining the University of Exeter (in 2014), most of his research has focused on studies to predict and prevent preeclampsia which, along with other health impacts, is a key risk factor for pre-term births.

Professor Wright was the statistician on two large international collaborative studies which have clearly demonstrated two key findings:

1. Collection and analysis of biomarkers and maternal factors at 1st trimester screening can effectively identify women at high risk of preterm preeclampsia (SPREE study) **[3.1].**
2. Taking low-dose aspirin in such high-risk pregnancies reduces the risk of preterm births by about two thirds (from 4.3% to 1.6%) (ASPRE randomised trial).

2.1. Analysis of patient and clinical datasets to develop predictive models for screening

In an initial study **[3.2]**, Wright and others used data from over 35,000 pregnancies at two UK hospitals to develop a competing risks model that was able to predict 75% (95% confidence interval 70-80%) of preterm preeclampsia, with a false positive rate of only 10%. These prediction models, that make use of biomarker data, almost doubled the pre-term preeclampsia detection rate compared with using maternal factors and medical history alone. This result, and the underlying predictive model, has been subsequently validated in two other large data sets **[3.3]**

2.2. Effectiveness trial to prevent preeclampsia

In the international ASPRE study, conducted from 2014 to 2016, 1,776 women at high risk for pre-eclampsia based on first-trimester combined screening were randomised to either low-dose aspirin (150 mg daily) or placebo, from 11–14 weeks to 36 weeks' gestation **[3.4, 3.5]**. Professor Wright led the design of the study's statistical analysis and the dose of 150

mg was selected in line with evidence that a significant proportion (10–30%) of patients show aspirin resistance at higher doses. The ASPRE trial found that aspirin reduced the risk for preeclampsia before 37 weeks by 62% (from 4.3% to 1.6%). Aspirin also reduced the risk of preeclampsia before 34 weeks by 82%, but this effect did not reach statistical significance due to the low absolute rates (0.4% vs 1.8%). The beneficial effect of aspirin appeared to depend on the degree of compliance, with the greatest risk reduction observed in women with compliance ≥90%.

Further research, based on the ASPRE trial, showed a reduction in the proportion of babies born before 32 weeks from 2.9% in the placebo group to 1.2% in the aspirin group. Of those admitted to the neonatal intensive care ward, the mean length of stay decreased by an average of 20 days and, overall, there was a reduction in length of stay of 68% (95% confidence interval, 20 - 86%) **[3.6].**

While Professor Wright has been the only Exeter researcher closely involved in this international collaborative research, he has played a pivotal role in their design, conduct and the dissemination of their findings (evidenced by first and second authorship on all the key academic publications). He developed the risk prediction algorithm used for the ASPRE and SPREE trial. He was the trial statistician for ASPRE and for the SPREE study with a key role in the original funding applications, study design, monitoring and the production of papers and other outputs from these studies. He has engaged with the diagnostic test companies (PerkinElmer, Thermo Fisher and GE) to facilitate implementation of prediction and prevention of preeclampsia worldwide. He is working with groups in Europe, the USA and Asia on implementation of these prediction and prevention strategies. Prior to the Covid 19 pandemic, he has been funded to visit Denmark, China, US and Israel to present his work at major scientific meetings and to support the implementation of prediction and prevention of preeclampsia.

3. References to the research

3.1. Poon LC, **Wright D**, Thornton S, Akolekar R, Brocklehurst P and Nicolaides KH. Mini-combined test compared with NICE guidelines for early risk-assessment for pre-eclampsia: the SPREE diagnostic accuracy study. *Efficacy Mech Eval* (2020);7(8). DOI 10.3310/eme07080

3.2. O'Gorman N, **Wright D**, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks gestation. *Am J Obstet Gynecol* 2016; 214: 103.e1–12. DOI: 10.1016/j.ajog.2015.08.034

3.3. Wright D, Tan MY, O'Gorman N, Poon LC, Syngelaki A, Wright A, Nicolaides KH. Predictive performance of the competing risk model in screening for preeclampsia. *Am J Obstet Gynecol* 2019; 220: 199.e1–13. DOI: 10.1016/j.ajog.2018.11.1087

3.4. Rolnik DL, **Wright D**, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Nicolaides KH. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol.* 2017; 50: 492–495. DOI: 10.1002/uog.18816

3.5. Rolnik DL, **Wright D**, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S,Maclagan K, Nicolaides KH.

Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; 377: 613–622. DOI: 10.1056/NEJMoa1704559

3.6. Wright D, Rolnik DL, Syngelaki A, Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. *Am J Obstet Gynecol* 2018;218:612.e1-6. DOI: 10.1016/j.ajog.2018.02.014

4. Details of the impact

Preeclampsia is a potentially serious condition experienced during pregnancy characterized by high blood pressure and associated possible organ damage. It affects up to 6% of pregnancies in the UK. In severe cases the health consequences for the pregnant woman can be fits (eclampsia), liver and blood clotting problems. In severe cases the consequences for the unborn child include pre-term birth (with associated complications such as neonatal respiratory distress syndrome), and a higher risk of stillbirth (death of baby after 24 weeks of completed pregnancy). Pre-term births, in turn, lead to increased risks of life-long impairments and physical and mental disabilities. In low- and middle-income countries it is one of the leading causes of maternal mortality and severe maternal morbidity.

Professor Wright's research on algorithms to predict, and the randomised trial of treatments to prevent preeclampsia, have led to decisive changes in clinical practice, and guidelines nationally and internationally.

4.1. Changing national clinical guidelines and practice

Evidence-based guidance on hypertension in pregnancy for the NHS in England and Wales was produced by the National Institute for Health and Care Excellence (NICE) in June 2019 (Guideline NG133) **[5.1]**. In section 1.1 (Reducing the risk of hypertensive disorders in pregnancy), recommendation 1.1.2 is "Advise pregnant women at high risk of pre-eclampsia to take 75–150 mg of aspirin daily from 12 weeks until the birth of the baby", and recommendation 1.1.3 is "Advise pregnant women with more than 1 moderate risk factor for pre-eclampsia to take 75–150 mg of aspirin daily from 12 weeks until the birth of the baby." The ASPRE trial is the only randomised trial to have shown the effectiveness and safety of low-dose aspirin in this patient group, and the NICE Guidance further states that "this use [of low-dose aspirin] is common in UK clinical practice" (p.37). As a result of the changes in guidelines, NHS clinicians have changed practice, as evidenced by testimonial **5.2;** '*the research of Professor Wright has had a clinically significant impact on changing our main health policy approach to tackle the problem of preeclampsia'*.

4.2. Changing international clinical guidelines

In 2018, both major international guidelines in this clinical field, from FIGO (*International Federation of Gynecology and Obstetrics*) **[5.3]** and ISUOG (*International Society of Ultrasound in Obstetrics and Gynecology*) **[5.4]**, changed their recommendations on screening for and treating preterm preeclampsia, directly citing both the risk prediction modelling and the ASPRE trial research findings by Wright as the basis for these changes. The research findings and recommendations have also been directly reflected in the 2019 ACOG guidelines (*American College of Obstetricians and Gynecologists*) **[5.5]**.

4.3. Changing the practice of obstetricians and gynaecologists internationally

As a direct result of the change in international clinical guidelines, screening for preeclampsia based on the FIGO and ISUOG guidance has been initiated in Asia, Australia, Europe and the US **[5.6]**. The screening algorithms make use of biochemical tests (of Placental Growth Factor), and the global company which manufactures and sells these tests (*PerkinElmer)* also has Professor Wright's pre-eclampsia risk prediction algorithms built into their own preeclampsia screening software **[5.7]**. *PerkinElmer* data demonstrates that the number of women receiving 1st trimester screening for preeclampsia has increased from 910,000 in 2017 to 2.6 million in 2019, following publication of the two key studies, and the resulting changes in international clinical guidelines (ISUOG 2018, FIGO 2019) (**Table 1**).

The estimate for 2020 is that 3.67 million trimester screens will use the algorithm, benefitting 2.6% of global pregnancies **[5.7].**

	ACTUAL SCREENS (millions)				PROJECTED (millions)	TOTAL (millions)
	2016	**2017**	**2018**	**2019**	**2020**	
CLINICAL TRIALS		ASPRE	SPREE			
GUIDELINES			ISUOG	FIGO		
Company 1	0.24	0.26	0.33	0.44	0.5	1.77
Company 2	0.075	0.145	0.25	0.42	0.45	1.34
Company 3	0.05	0.125	0.28	0.35	0.42	1.22
1st T screens excluding Biochemistry	0.125	0.375	0.85	1.4	2.3	5.05
TOTAL 1st Trimester Screens	**0.49**	**0.91**	**1.71**	**2.61**	**3.67**	**9.39**
Global pregnancies	140	140	140	140	140	700
% of Global Pregnancies screened	**0.35%**	**0.65%**	**1.22%**	**1.86%**	**2.62%**	**1.34%**

Table 1. Perkin-Elmer data on the supply of biochemical test kits by three companies.

The Vice President for Market Development for the Reproductive Health Business of PerkinElmer Inc further stated: "*The top 6 countries today for PerkinElmer [placental growth factor] Kit sales are Canada Russian Federation, China, South Korea, Australia and India. … The algorithm developed by Prof Wright is very flexible, enabling widespread adoption by High Income Countries and Low-Middle-Income Countries (LMIC). It is possible to screen for pre-term [preeclampsia] at the simplest level by utilising maternal history and blood pressure only, both of which are readily available in LMIC".* (page 1 of source **5.7**).

First-trimester screening and intervention with aspirin is cost-effective, combining the prevention of a significant proportion of early-onset cases of preeclampsia with cost savings to health systems (Ortved et al 2018, **[5.8]**) For the NHS in England and Wales, combining the ASPRE trial outcome data on mean length of stay in neonatal intensive care (mean reduction of 1.4 days, NHS cost per day in intensive care £1,513 **[5.9, 5.10]**) with the estimated proportion of pregnant mothers screened as high risk (10% = 65,000 pregnancies per year **[5.11]**), suggests that after deducting the cost of taking aspirin during pregnancy (£14 per 25 week course) this treatment would yield estimated net NHS savings across all affected births in England and Wales of about £130 million per year (estimated for 2019).

Globally, the estimated healthcare cost savings are far larger. An analysis by *PerkinElmer*'s marketing department estimates an increase in global healthcare cost savings from $301 million to $1,392 million between 2017 and 2020, again assuming that the 10% of pregnancies identified as high risk take low-dose aspirin (**Table 2** from evidence **5.7**). By the end of 2020 they estimate that 49,400 cases of preeclampsia will have been prevented due to the screening and aspirin treatment introduced as a result of Professor Wright's research.

	2016	2017	2018	2019	2020	TOTAL
Women screened globally (millions)	0.49	0.905	1.71	2.61	3.67	**9.38**
Women identified as high risk (10%) and treated with aspirin (thousands)	49	90.5	171	261	367	**938**
Women with preterm PE (assume 1% prevalence globally), who are detected (average 70%) (thousands)	3.4	6.3	12.0	18.3	25.7	**65.7**
Number of cases of PE avoided (<37 weeks GA) 75% of those detected based on 90% compliance to Aspirin (thousands)	2.6	4.8	9	14	19	**49.4**

Healthcare savings: NICU costs alone (average 20 days per case avoided) at average $1300 per day (range $275 (India) - $3000 USA) (millions)	$67.6	$301	$534	$891	$1,392	**$3185**

Table 2. PerkinElmer analysis of healthcare savings. PE = preeclampsia.

5. Sources to corroborate the impact

5.1. NICE Guideline [NG133]: Hypertension in pregnancy: diagnosis and management. National Institute of Health and Care Excellence. 25th June 2019. https://web.archive.org/web/20201217113128/https://www.nice.org.uk/guidance/ng133

5.2. Letter of testimony from Consultant and Director, Fetal Medicine Unit, St Georges Hospital, London, stating that Professor Wright's research has had a significant impact on their clinical practice.

5.3. FIGO guideline for first trimester screening and prevention of preeclampsia. [Agreed and presented December 2018, PowerPoint slideset]. Full publication awaited. DOI: 10.1002/ijgo.12802

5.4. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc, Khalil A, Martins WP, Odibo AO, Papageorghiou AT,Salomon LJ, Thilaganathan B. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound Obstet Gynecol 2018. DOI:10.1002/uog.20105

5.5. ACOG. (American College of Obstetricians and Gynecologists) Gestational Hypertension and Preeclampsia. *Practice Bulletin Number 202*, January 2019.

5.6. Letter of testimony from Obstetrician at Mount Sinai Hospital, University of Toronto describing implemention of Dr Wrights' multiple marker algorithm to screen all pregnant women for early preeclampsia at Mount Sinai Hospital.

5.7. Letter of testimony (29th September 2020) from Vice President for Market Development for the Reproductive Health Business of PerkinElmer Inc.
Contains the company's estimates of both their own and competitor company use of the screening algorithms (Table 1), and a related estimate of global healthcare cost savings (Table 2) as a result of the combined introduction of the preeclampsia screening and treatment with aspirin.

5.8. Ortved D, Hawkins TL, Johnson JA, Hyett J, Metcalfe A. Cost-effectiveness of first-trimester screening and early preventative use of aspirin in women at high risk of early-onset pre-eclampsia. *Ultrasound Obstet Gynecol* 2018. DOI: 10.1002/uog.19076

5.9. Wright D, Rolnik DL, Syngelaki A, Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. *Am J Obstet Gynecol* 2018;218:612.e1-6. DOI: 10.1016/j.ajog.2018.02.014

5.10. Department of Health. NHS National Schedule of Reference costs 2018 to 2019 [Dataset]. NHS Improvement; 2019 [updated 19 February 2020]. Available from: https://web.archive.org/web/20201217114333/https://www.england.nhs.uk/national-cost-collection/.

5.11. Office of National Statistics. Births in England and Wales: 2018.