Hello. My name is Andrei Morgan, and today I'm going to talk to you about the WP7 demonstration project on extreme preterm birth.

In this presentation, I will show to you first of all the background to this study, talking about how it provides an opportunity to conduct research across different countries, and I will talk in specific detail about the three cohorts that are included. I will then go into further detail about the methods – particularly the data harmonisation that was carried out, and the statistical analyses – before presenting to you the results. Finally, as a summary, I will discuss a little bit about the project and I will highlight some learning points and then provide you with some further reading to explore at your own leisure.

The context of this study was that we know that there is important variation between high-income countries in the survival of babies born at 22 to 26 weeks of gestational age. As Rolf presented to you earlier on in the course, we don't know quite why these differences exist. They could exist because of differences in decision-making and the management between the different countries; it may also be that there are differences in the different populations that are included in the different studies; and, finally, there are also other, methodological issues such as differences in the variable definitions that may contribute to the differences that are seen. So, by using individual patient data, and bringing the data together, we're able to perform a real comparison to really explore the issues. Specifically, we wanted to answer the questions: when do the differences in survival occur, and can we identify any specific influencing factors?

The first cohort that we used data from was the EXRESS cohort. This is a geographical birth cohort of all births occuring at less than 27 weeks of gestational age, and the data were collected over a 3 year period in Sweden, between 2004 and 2007. There was prospective data collection, with linkage being performed with the National Birth Registry to verify the maternal and the neonatal data, and linkage with the National Population Registry to verify the survival up to 1 year of age. The children – the surviving children – were then followed-up at 2 ½ years of age.

The second cohort was the EPICure-2 cohort. This, again, was a geographical birth cohort, collecting data on all births at less than 27 weeks of gestational age over a 1 year period, and the study investigators collected data on English babies which they defined as those babies who were born to mothers who are normally resident in England. Therefore, they excluded parents from Scotland or Wales who may have delivered just over the border. There was again prospective data collection; the investigators collected data on a postnatal form relating to the pregnancy, labour and delivery of all births, and then for those babies that were admitted into the intensive care units, further data were collected on a case record form for each child, and follow-up was performed at 3 years of age.

The final cohort is the EPIPAGE-2 cohort. Again, this is a geographical birth cohort, prospectively collected, of births in France. This time the investigation included births occuring at 22 to 34 weeks of gestational age, but we're only going to use the births that occurred at less than 27 weeks of gestational age, and these were collected over an 8 month period, and included babies that were born in what are known as the DOM-TOMs which are the overseas terroritories that are also part of France. There was again prospective data collection with detailed questionnaires for the mothers-to-be, and about the pregnancy for the doctors, and then detailed questionnaires for the babies that were admitted into intensive care, and follow-up was performed at 2 years of age.

In order to harmonise the data, we first had to harmonise the populations, and so we excluded terminations of pregnancy and we excluded out of hospital births, and we included several different baseline populations to ensure that we were including the same information for each of the cohorts. First of all, we used the fetuses alive at maternal admission to hospital, then we took the live births, then we took the babies surviving to 1 hour of age, and then we took the babies surviving to 24 hours or 1 day of age. Then the babies surviving to 7 days of age. And finally we examined the population of babies surviving to 28 days of age. We also harmonised the variables, focussing on population and pregnancy characteristics, as well as looking at the antenatal and postnatal management, and the neonatal and longer-term morbidities. In this study I'm going to focus on – or, in this presentation, I'm going to focus on, the survival, and so we're going to mainly use the population and pregnancy characteristics.

The statistical analysis included this data harmonisation that I've just described, and we then performed a descriptive analysis, and because there were very few births – or, very few survivors – at 22-23 weeks of age, we grouped these two gestational age groups together, and then looked at 24 week, 25 week and 26 week births separately. We performed Kaplan-Meier analysis that was stratified by the gestational age in weeks, and we censored it at 112 days, which is equivalent to 16 weeks of chronological age, and is round about the term gestation, and we performed the analysis according to the landmark times that were according to the populations I described earlier. I then performed a Cox proportional hazards regression analysis, and this included clustering by the mother to account for the effects of multiple births where thetwins or the triplets may share the same intra-uterine environment and therefore have exposure to similar environmental factors, and performed adjusted and, well unadjusted and adjusted analyses, and the adjusted analyses were adjusted for maternal age, parity, pre-existing diabetes and hypertension, pre-eclampsia, placental abruption, spontaneous labour, multiple pregnancy, sex, and birth weight. And we examined the Schoenfield residuals to assess that the proportional hazards assumption was met.

The results now. So there were 3471 mothers with 4438 live fetuses at admission to hospital: 769 of these fetuses were in the EXPRESS, 2310 in EPICure-2 and 1359 in EPIPAGE-2, and we noted important differences in maternal age, parity, multiple status, pregnancy-induced hypertension, placental abruption, the rate of congenital anomalies, the onset of labour, and antentatal steroid exposure and delivery mode between the three populations, but there were no important differences in the levels of pre-existing diabetes or hypertension amongst the mothers, or in the fetal sex or the birth weights of the babies that were born at each gestational age. I am not going to report the Cos regression because the adjusted results were consistent with the Kaplan-Meier plots which you will see on the next few graphs.

So this is the first slide and it shows you the data, the results for those babies that were born or those births that occurred at 22 to 23 weeks of gestation. I will go through this relatively slowly because the next slides are similar. Here in the top left, you have a graph that shows the survival for the fetuses alive at maternal admission to hospital. The red line represents survival for the fetuses alive at 22 to 23 weeks of gestation in the EXPRESS study; the green line, which is the middle one, shows the results for the EPICure study; and the blue line shows those for the EPIPAGE 2. We can see here that the EXPRESS had the best survival, at around about 20… 30% say, with EPICure having survival at around, probably about 12%, and EPIPAGE having virtually no survival at for the fetuses who were alive at maternal admission. The next graph at the top, in the middle, shows the same kind of results but for those babies who were born alive. The one on the right at the top shows the same results but for those babies who survived to 1 hour of age. And we move to the bottom, we can see the results on the left show the results for those, the baseline

population being the babies who survived to 24 hours of age; the middle graph shows the baseline population being the children that survived to 7 days of age; and the last diagram on the very right at the bottom, shows survival for those children who were alive at 28 days of age. On the bottom, we have what's known as a *risk table*, and this shows the numbers that are alive at each point in time. And what we can see just by jumping to the end is that survival is quite poor compared to the beginning, but it's particularly poor in EPIPAGE: you see that there are only 2 survivors at 16 weeks of age from the 366 fetuses that were alive at maternal admission to hospital, and most of these die either at birth, or in the first hour or so following delivery. And that explains why what we see on the graphs, particularly the bottom graphs, there are some jagged lines, and actually 100% survival for those who survive to 28 days of age, and we don't have very much confidence in this because there are essentially only 2 children who survive to 28 days of age, and these children both survive to 16 weeks or 112 days of age, although one of them subsequently died prior to discharge from hospital. So what we do see is that there is important differences at each of these time points,

I'm now going to move just to the next graph, and this shows the results for 24 weeks of gestation. And the first thing that strikes us, just moving from one slide to the next – I'm going to go back, and forwards, and back, and forwards – and we can see for all of those, that the survival at this gestational age, at 24 weeks of gestation, is better than at 22 and 23 weeks of gestation, regardless of the starting population. What we also notice is that the order is generally the same, so the survival is best in the EXPRESS cohort, which is always at the top, followed by EPICure followed by EPIPAGE which has the poorest survival, so the poorest survival happened in the French cohort in 2011, and the best survival occurred in the Swedish cohort that had data collected in 2004 to 2007. However, we see something that is quite interesting: there are marked differences in the first few populations, through to 1 hour of age, and then even at 24 hours of age it's possible to distinguish between the 3 cohorts. However, by the time we get to 7 days of age, the blue and the greens, so the EPIPAGE-2 and the EPICure-2 survival curves are essentially identical, and there is no longer a difference between these two cohorts. And this is exactly the same in the population of babies that survived to 28 days of age.

Moving onto 25 weeks, we see a very similar picture again: the survival is better than it was at 24 weeks of gestation at all of these different time points, there are still the differences between the 3 different cohorts, with survival the best in the EXPRESS cohort and the poorest in the EPIPAGE-2 cohort, although by looking at the population of children that survive to 28 days of age, we basically see no differences and the p-value for this graph is 0.51, so there are no differences between any of the cohorts.

And, at 26 weeks of age, again, the same sort of thing: we see that the survival is better than it was at 25 weeks in all of the cohorts, the EXPRESS cohort still has the best survival, and actually by the time we get to 1 week of age, the differences between the cohorts have essentially disappeared – there is perhaps a slight advantage in the Swedish cohort, but it's quite minimal compared to previously. And even in the populations that survive to 1 day of age, the p-value for the difference between the cohorts is 0.065, so it's not quite reaching statistical significance at less than 0.05, and you could say that probably, there is not much of a difference between these cohorts.

So, in summary, I've showed you a survival study comparing individual patient data from 3 different European cohorts looking at survival of extreme preterm babies. The strengths of this study is that we used population cohorts, with detailed harmonisation of the variables, robust statistical methods, and absolutely minimal missing data. However, there are some limitations, as

ever, and in this study, two of the major limitations are that there was that there was a lack of common socio-economic variables that we were able to compare, and there has also been a relatively large time delay since the cohorts, and they're all historical, and the most recent cohort is already 10 years old. The study confirms previous research in that it shows there is wide variation in survival for extremely preterm births, and that survival improves with gestational age, and it extends our knowledge by showing that variation persists over time when using different baseline populations, so whetehr that is the fetuses who are alive at maternal admission to hospital, the population of live births, or even the populations of babies that have survived to 1 hour of age, or 1 day of age, or 7 days of age. In conclusion, there are large differences in survival that occur during labour and the first hours and days after birth, and early active management is reflected in higher survival at key census points right through to 112 days of postnatal age.

So, a few learning points. First of all, how can we investigate differences in outcomes for extremely preterm births? Well, detailed harmonisation of the data sets is required, and advanced statistical techniques can be used with individual patient data. When do these survival differences occur? They are most pronounced early on at all gestational ages, but they continue to be evident over the first days and weeks of life. Finally, what factors explain the differences? Well, we found that population characteristics did not explain the survival differences, and we feel that social-economic and ethnicity factors are unlikely to explain all the remaining variation, even if they play some small contributory role. Therefore, this leaves us with a final, major explanation, that is the variation in societal choices that occur between the 3 countries.

Finally, I leave you with just a little bit of reading, a little bit of further information about each of the cohorts. I have listed here on this slide the main papers for the EXPRESS, EPICure-2 and EPIPAGE-2 cohorts describing the baseline survival of the birth cohorts, and the initial follow-ups that occurred at 2 ½, 3 years and at 2 years in the EXPRESS, EPICure-2 and EPIPAGE-2 cohorts, respectively. Thank you for listening.