PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Management of patent ductus arteriosus in very preterm infants in England and Wales – a retrospective cohort study
AUTHORS	Ojha, Shalini Al-Turkait, Asma Szatkowski, Lisa Choonara, Imti

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	21-Jan-2022

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. These were generally fine, and I have only a couple of comments. General: The authors appear to have data on the entire population. When this is so, the use of inferential statistics (p values and CIs) is controversial. Many statisticians (including me) feel that they don't make much sense, as there is no population to infer to - you have the whole population. Others think that it makes sense to posit a "super population" of some sort. I'd recommend removing p values and CIs from the tables, and I commend the authors for not using them in the text. But, if the authors want to posit a superpopulation, that's fine, they just need to mention what they are doing. p. 8 line 45 (and other places) - insert "significant' or "significantly" as appropriate Peter Flom

REVIEWER	Reviewer name: Dr. Omer Erdeve Institution and Country: Ankara University Faculty of Medicine, Turkey Competing interests: None
REVIEW RETURNED	05-Feb-2022

GENERAL COMMENTS	Electronic patient data recorded at participating neonatal units that collectively form the United Kingdom Neonatal Collaborative which are transmitted to the Neonatal Data Analysis Unit to form the National Neonatal Research Database (NNRD) were used to have idea on PDA diagnosis and treatment choices İn England and Wales. Although this is an observational study, adds information on chronological management of PDA. I have few major concerns: 1. 'the 16,440 infants with PDA, 34.8% (n=5,721; 9.8% of total <32 weeks' infants included) received a PDA-specific treatment (indomethacin and/or ibuprofen and/or surgery) decreasing from 41.3% in 2010 to 33.7% in 2017.' is

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	stated. The major finding according to me is that decrease in PDA treatment rate by time. This should be stated at what this study adds section. 2. By the way, the figure's B section does not show a decline in PDA management, please check it. 3. Do you have any idea about conservatively managed patients as there is a decrease in treatment rate. 4. Recent PDA-Tolerate and INTER-PDA studies may add current comment in discussion on conservative management which gains popularity among NICUs. Okulu E et al. An Observational, Prospective, Multicenter, Registry-Based Cohort Study Comparing Conservative and Medical Management for Patent Ductus Arteriosus. Front Pediatr. 2020 Jul 31;8:434. Clyman RI, et al. PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age. J Pediatr. 2019 Feb;205:41-48.e6. doi: 10.1016/j.jpeds.2018.09.012. Epub 2018 Oct 16. PMID: 30340932; PMCID: PMC6502709. 5. Treatment is seen to increase the rates of NEC, LOS, and death but decreases BPD. I believe that those should be discussed with secondary analyses of PDA-Tolerate study. 6. What about side effect profiles between treatmnt choices, a table can be added.

REVIEWER	Reviewer name: Dr. Souvik Mitra Institution and Country: Dalhousie University Faculty of Medicine, Canada Competing interests: None
REVIEW RETURNED	10-Feb-2022

GENERAL COMMENTS	Al-Turkait and colleagues have conducted a retrospective cohort study using routinely recorded data from the National Neonatal Research Database of infants born at <32 weeks admitted to neonatal units in England and Wales to describe the diagnosis and treatment characteristics of PDA between 2010 to 2017. Overall, the authors concluded ibuprofen was the preferred drug and surgical interventions were observed to be less frequent for PDA closure among very preterm infants in England and Wales. The paper is clearly written. There are several methodological constraints in this paper that have been highlighted. The paper may further benefit from further addressing the following limitations: Abstract The authors acknowledge their limitations in the main paper, some of which are major, such as inability to clearly establish a diagnosis of PDA. Given the nature of such limitations, at least the fact that there was no echocardiographic confirmation of the PDA, should be highlighted in the study design section of the abstract as well. Methods 1. Exclusion criteria: Could the authors explain why were late admissions or those with extreme birth weight for GA excluded? 2. Lack of echocardiographic diagnosis of the PDA remains a major limitation of the paper. Could the authors tease out the proportion of infants who had an echocardiographic confirmation of PDA and conduct a sensitivity analysis of medication use/surgery and their association with clinical outcomes? 3. Could the authors confirm that none of the infants included in this cohort had prophylactic therapy with NSAIDs for IVH prevention initially and subsequently got diagnosed with PDA, that remained untreated? Because, this cohort would not technically fall under the group of "received NSAIDs for PDA". 4. Majority of clinicians have moved away from treating PDA in more mature preterm infants, ie, born between 28-32 weeks. While controversy still exists on if and when to treat PDAs in extremely

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	preterm infants (<28 weeks GA). Therefore, a subgroup analysis in this particular gestational age group will be of interest for clinicians and might generate important hypotheses for future clinical trials. 5. Given that paracetamol may be used for other indications in infants who may also happen to have a PDA, is it fair to include paracetamol along with indomethacin and ibuprofen which are PDA specific when defining the "PDA treated" cohort? 6. Please mention the covariates entered in the multivariable regression model in the methods section. Discussion 1. On page 14 the authors mention: "we found that more infants who died during neonatal care did not have a PDA". Is this statement correct? Table 1 suggests 11.6% of infants with PDA died versus 8.3% infants without PDA. However, the direction of effect seems to be reversed after adjustment for potential confounders in the multivariable analysis. While, such reversal may occasionally happen due to a strong confounding effect of a covariate, such occurrences are rare in neonatal literature. Therefore, this finding deserves an explanation, as to why the direction of effect for death was reversed on multivariable regression. 2. Moreover, the survival bias rationale in the following sentence used to explain increased deaths among those who did not have PDAs may not hold true as table 1 suggests more deaths occurred among infants who did have a PDA. 3. The authors mention: "Infants who survived were more likely to have undergone a clinical or echocardiographic evaluation resulting in a diagnosis of PDA as compared to those who did not live long enough for such a diagnosis to be made": Does this mean that infants who died prior to the diagnosis of PDA being made were also included in the analysis? Shouldn't these infants be excluded from the analysis?

VERSION 1 – AUTHOR RESPONSE

Thank you for reviewing our manuscript. We have considered all the comments and made changes to the manuscript accordingly. Please see the changes in the tracked version of the manuscript in addition to the responses below.	
Comment	**Response**
Associate Editor	
the comment on the figure (reviewer 2) should also be considered as this suggest that the current 'visualisation and presentation of the data' is not yet sufficiently clear to the readership	Thank you. We have done this. Please see below, in line with Reviewer 2's comment.
Reviewer 1: Dr. Peter Flom, Peter Flom Consulting	
I confine my remarks to statistical aspects of this paper. These were generally fine, and I have only a couple of comments.	Thank you.
General: The authors appear to have data on the entire population. When this is so, the use of inferential statistics (p values and CIs) is controversial. Many	The p-values have been presented here as we believe there is a larger population of infants outside of England and Wales such

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statisticians (including me) feel that they don't make much sense, as there is no population to infer to - you have the whole population. Others think that it makes sense to posit a "super population" of some sort. I'd recommend removing p values and CIs from the tables, and I commend the authors for not using them in the text. But, if the authors want to posit a superpopulation, that's fine, they just need to mention what they are doing.	as in other UK-nations, Europe and North America where our findings are applicable.
p. 8 line 45 (and other places) - insert "significant' or "significantly" as appropriate	Added “significantly”
Reviewer 2: Dr. Omer Erdeve, Ankara University Faculty of Medicine	
Electronic patient data recorded at participating neonatal units that collectively form the United Kingdom Neonatal Collaborative which are transmitted to the Neonatal Data Analysis Unit to form the National Neonatal Research Database (NNRD) were used to have idea on PDA diagnosis and treatment choices İn England and Wales. Although this is an observational study, adds information on chronological management of PDA.	Thank you.
1. 'the 16,440 infants with PDA, 34.8% (n=5,721; 9.8% of total <32 weeks' infants included) received a PDA-specific treatment (indomethacin and/or ibuprofen and/or surgery) decreasing from 41.3% in 2010 to 33.7% in 2017.' is stated. The major finding according to me is that decrease in PDA treatment rate by time. This should be stated at what this study adds section.	Thank you. We have added this: “Among those who had a PDA, 35% received PDA-specific treatment. The percentage of infants receiving PDA-specific treatment decreased from 41.3% in 2010 to 33.7% in 2017.”
2. By the way, the figure's B section does not show a decline in PDA management, please check it.	Thank you. To ensure clarity, we have divided the figures further and changed the scale of the Y-axis to ensure the changes are visible: please see edited version of Figure 1 and the figure legend. In the panels that show the percentage treated, we have removed the line that showed paracetamol as this drug is not included in our analysis of those who received PDA-specific treatment and added

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	a line that shows the percentage who received any treatment (i.e., indomethacin and/or ibuprofen and/or surgery) where a decline is clearly visible. We have also given details in the text to ensure that the changes are explained clearly. "Figure 1, panel A and B show the percentage of all very preterm infants who were deemed to have a PDA by gestational age week at birth and year of birth, respectively. Highest percentages of infants with a diagnosis of PDA was among those born at 24 weeks' (70.2%) and 25 weeks' (70.5%) GAs reducing to 6.1% of 31 week infants. There was an increase in the percentage of infants with a PDA from 25.5% in 2010 to 28.5% in 2017." AND "Figure 1 (panels C and D) represents treatment by gestational age week at birth and by year of birth, respectively. It shows that the overall percentage of infants who received any treatment (ibuprofen and/or indomethacin and/or surgery) decreased from 41.3% in 2010 to 33.7% in 2017. In the same period, the use of ibuprofen increased from 20.2% to 27.3% while use of indomethacin decreased from 20.0% to 8.8%. Surgical closure of PDA decreased from 9.1% to 3.0%. "
3. Do you have any idea about conservatively managed patients as there is a decrease in treatment rate.	We do not have data on this. The database does not record those who were treated conservatively. We can make an estimate by looking at how many had a diagnosis recorded but did not receive ibuprofen/indomethacin or have surgery but this will not be accurate as many cases may not have been recorded if no treatment was given. We have added a section in the discussion: "We did not have the information to determine how the diagnosis was established. Infants with a PDA that was hemodynamically insignificant and was not treated may not have the diagnosis entered in the database."

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4. Recent PDA-Tolerate and INTER-PDA studies may add current comment in discussion on conservative management which gains popularity among NICUs. Okulu E et al. An Observational, Prospective, Multicenter, Registry-Based Cohort Study Comparing Conservative and Medical Management for Patent Ductus Arteriosus. Front Pediatr. 2020 Jul 31;8:434. Clyman RI, et al. PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age. J Pediatr. 2019 Feb;205:41-48.e6. doi: 10.1016/j.jpeds.2018.09.012. Epub 2018 Oct 16. PMID: 30340932; PMCID: PMC6502709.	Thank you for highlighting these publications. We have included them in them in the discussion and introduction. "Similarly, Okulu et al., [11] reported that in the cohort of 1,193 infants born at 24 to 28 weeks' gestation, 24% with echocardiographically-confirmed moderate-to-large PDA were managed conservatively. Although they did not find any difference in the rates of BPD, infants who were treated had a higher rate of death (OR (95% CI), 1.82 (1.15 to 2.89) when compared to those who were not treated [11] similar to our finding that the adjusted odds of death before discharge was lower among the infant with PDA who did not receive treatment, particularly among the extremely preterm infants (aOR (95% CI), 0.59 ((0.53 to 0.66))." "Randomised controlled trials (RCTs) show that routine early treatment does not reduce PDA ligation or clinical outcomes and may be associated with higher rates of adverse events."
5. Treatment is seen to increase the rates of NEC, LOS, and death but decreases BPD. I believe that those should be discussed with secondary analyses of PDA-Tolerate study.	We have added a section in the discussion about the lower odds of death and BPD in our treated group when compared to the untreated infants and added the following to the discussion: "The recent PDA-TOLERATE trial [5] reported more deaths among those who received early routine treatment as compared to those who were treated conservatively although the difference was not statistically significant."
6. What about side effect profiles between treatmnt choices, a table can be added.	We do not have data on the side effects and adverse events and hence did not touch upon those.
Reviewer: 3 **Dr. Souvik Mitra, Dalhousie University Faculty of Medicine, IWK Health Centre**	
Al-Turkait and colleagues have conducted a retrospective cohort study using routinely recorded data from the National Neonatal Research Database of	Thank you.

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infants born at <32 weeks admitted to neonatal units in England and Wales to describe the diagnosis and treatment characteristics of PDA between 2010 to 2017. Overall, the authors concluded ibuprofen was the preferred drug and surgical interventions were observed to be less frequent for PDA closure among very preterm infants in England and Wales. The paper is clearly written. There are several methodological constraints in this paper that have been highlighted. The paper may further benefit from further addressing the following limitations:	
Abstract The authors acknowledge their limitations in the main paper, some of which are major, such as inability to clearly establish a diagnosis of PDA. Given the nature of such limitations, at least the fact that there was no echocardiographic confirmation of the PDA, should be highlighted in the study design section of the abstract as well.	We have edited the first line of the results in the abstract to reflect this: "Among 58,108 infants born at <32 weeks' GA, 28.3% (n=16,440) had a PDA diagnosed clinically or with echocardiographic confirmation." We have added the following to the methods section where we describe how the PDA diagnosis was ascertained: "We did not have sufficient information to determine how the PDA was diagnosed i.e., whether the diagnosis was confirmed by an echocardiogram or made based on clinical signs and symptoms only." And in the discussion: "We did not have the information to determine how the diagnosis was established."
Methods 1. Exclusion criteria: Could the authors explain why were late admissions or those with extreme birth weight for GA excluded?	When using the NNRD, we typically exclude these cases as they are markers of poor data integrity. All very PT infants are admitted to a neonatal unit within hours (or less) of birth. Admission records of very PT infants that do not include the first day means that their first admission record is missing, and key baseline data may not be correct. Also, data on diagnoses and treatments on the first day of life will be missing. Hence such cases are excluded. We exclude birth weight extremes similarly as they are unlikely to be correct (possible but unlikely) and incorrect data on key

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	characteristics (such as birth weight) indicate that the other data may also be questionable. We have followed the same methodology in previous publications. [1–3]
2. Lack of echocardiographic diagnosis of the PDA remains a major limitation of the paper. Could the authors tease out the proportion of infants who had an echocardiographic confirmation of PDA and conduct a sensitivity analysis of medication use/surgery and their association with clinical outcomes?	Unfortunately, the NNRD does not provide this information.
3. Could the authors confirm that none of the infants included in this cohort had prophylactic therapy with NSAIDs for IVH prevention initially and subsequently got diagnosed with PDA, that remained untreated? Because, this cohort would not technically fall under the group of "received NSAIDs for PDA".	The indication of drug use is not given in the NNRD hence this is not possible for us to do. We have assumed that the use for indomethacin, even when used as prophylaxis for IVH, can close the PDA. We have added this to the discussion to explain that this is a possibility and yet we decided to retain those cases as indomethacin, even when given as prophylaxis for IVH, reduced the need for further PDA treatment. "Similarly, it is possible that some use of indomethacin, particularly when given on the first day after birth, may have been for prevention of intraventricular haemorrhage and not following a PDA diagnosis although such treatment may then have reduced the possibility of the infant needing further treatment for PDA[9]"
4. Majority of clinicians have moved away from treating PDA in more mature preterm infants, ie, born between 28-32 weeks. While controversy still exists on if and when to treat PDAs in extremely preterm infants (<28 weeks GA). Therefore, a subgroup analysis in this particular gestational age group will be of interest for clinicians and might generate important hypotheses for future clinical trials.	Thank you for this suggestion. We have added subgroup analyses: Tables 2&3: Characteristics and outcomes of infants with and without a PDA And Tables 4&5: Characteristics and outcomes of infant with a PDA who received and those who did not receive treatment
5. Given that paracetamol may be used for other indications in infants who may also happen to have a PDA, is it fair to include paracetamol along with indomethacin and ibuprofen which are	We didn't include paracetamol as defining the treated cohort for the purposes of comparing treated and untreated – please see our description of methods: "The characteristics and clinical outcomes of infants with PDA who were treated and

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PDA specific when defining the “PDA treated” cohort?	those who were not treated with indomethacin and/or ibuprofen, and/or surgery are described and compared in Table 3.” We have now also added an additional sensitivity analysis, whereby infants with a diagnosis of PDA but who only received paracetamol (and not indomethacin/ibuprofen/surgery) were excluded from analysis rather than being included in the untreated group. Results were similar, but in the sensitivity analysis infants who were treated also had a higher odds of NEC. We have described this in our methods and results sections. Addition to methods: “Given uncertainty about the indication for paracetamol use, infants with of PDA but whose only treatment was paracetamol were classified as untreated. In a sensitivity analysis we excluded these infants from the comparison and conducted a comparison between those who received treatment with indomethacin and/or ibuprofen and/or surgery and those who had no treatment excluding those who had treatment with paracetamol only.” Addition to results: “In the above analyses, among the infants in the group that was designated as not having received PDA treatment, there were 2,209 infants who had received at least one dose of paracetamol sometime during their care. It is possible that some of this may have been for treating PDA. Therefore, we performed a sensitivity analysis where infants who only received paracetamol were excluded. The results were similar except that more treated infants had NEC (n=433/5,721, 7.6%) when compared to those who were not treated (n=334/8,8510, 3.9%) giving a higher adjusted odds of NEC in the treated group (aOR 1.25, 95% CI 1.07-1.47).”

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6. Please mention the covariates entered in the multivariable regression model in the methods section.	Our analyses were adjusted for sex, gestational age at birth in completed weeks and birthweight z-score <-2SD vs >=-2SD. These were previously included as a footnote to Table 1 and we have also now added this detail to our methods section.
Discussion 1. On page 14 the authors mention: "we found that more infants who died during neonatal care did not have a PDA". Is this statement correct? Table 1 suggests 11.6% of infants with PDA died versus 8.3% infants without PDA. However, the direction of effect seems to be reversed after adjustment for potential confounders in the multivariable analysis. While, such reversal may occasionally happen due to a strong confounding effect of a covariate, such occurrences are rare in neonatal literature. Therefore, this finding deserves an explanation, as to why the direction of effect for death was reversed on multivariable regression.	Thank you for this comment. We need to explain this further. The reversal of odds is due to adjustment for confounders and on further interrogation of data, we believe that the main effect is of GA. We have explained this further in the results section by adding the following: "Although the percentage of infants who died before discharge was higher among those who were deemed to have a PDA (11.6%) than among those who did not have a PDA (8.3%), after adjustment for confounders, the odds of death were reduced in the group that was deemed to have PDA (aOR (95% CI), 0.30 (0.27 to 0.32). This may be because of adjusting for GA at birth. Among infants born at 24- and 25-weeks' GA, 70% had a PDA and 40% died while at the other end, at 31 weeks' GA, 6% had a PDA and <2% died. After accounting for the high risk of death at the lower gestational ages and other confounders, a diagnosis of was PDA was associated with a lower odds of death before discharge."
2. Moreover, the survival bias rationale in the following sentence used to explain increased deaths among those who did not have PDAs may not hold true as table 1 suggests more deaths occurred among infants who did have a PDA.	Thank you. We agree. In the sub-group analysis that you suggested, show that among <28 weeks' GA infants, death before discharge was higher among those with without a PDA diagnosis (34.5%) than in those without a PDA (15.6%) and the aOR was 0.21 (0.19 to 0.23). These results are added (Table 3 and text in the results section). We have modified the mention of survival bias in the discussion section to reflect on this finding. "In the subgroup analysis including only the extremely preterm infants, we found that the percentage who died was significantly higher in the group that did not have a PDA and the adjusted odds of death remained statistically significantly higher in that group even after adjustment for GA. We did not

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	exclude early deaths and infants who survived were more likely to have undergone a clinical or echocardiographic evaluation resulting in a diagnosis of PDA as compared to those who did not live long enough for such a diagnosis to be made. We have reported similar confounding in other reports[10] and such survival bias is a recognised limitation of observational studies particularly in a population such as extremely preterm infants where there is a high risk of early deaths."
3. The authors mention: "Infants who survived were more likely to have undergone a clinical or echocardiographic evaluation resulting in a diagnosis of PDA as compared to those who did not live long enough for such a diagnosis to be made": Does this mean that infants who died prior to the diagnosis of PDA being made were also included in the analysis? Shouldn't these infants be excluded from the analysis?	As mentioned above, we did not exclude early deaths as were interested in overall mortality. There is no specified cut-off for defining early deaths for such exclusions. Many infants, especially extremely preterms, have early ECHOs and would have an established diagnosis of PDA (and may even have received treatment) within hours of birth. We therefore opted to keep all infants in the cohort and acknowledge that this may have affected the comparisons, particularly for the outcome death before discharge. Hence, the acknowledgement of potential survival bias and as given above, we have clarified this further.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	22-Feb-2022

GENERAL COMMENTS	The authors have addressed my concerns and I now recommend publication.

REVIEWER	Reviewer name: Dr. Omer Erdeve Institution and Country: Ankara University Faculty of Medicine, Turkey Competing interests: None
REVIEW RETURNED	27-Feb-2022

GENERAL COMMENTS	Authors have stated my suggestions and responded totally. I recommend its publication.

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