Diagnostic Utility of Lung Ultrasound in Preterm Neonates with Respiratory Distress at a Tertiary Neonatal Intensive Care Unit in the Western Cape

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THESIS FORMAT

This dissertation complies with the University of Cape Town's Publication-ready Manuscript formatting requirements.

The Publication-ready Manuscript has been formatted according to author guidelines for the journal, **Pulmonary Therapy**, a journal tracked by the Institute for Scientific Information (ISI), with an impact factor of 3.0 in 2022. The journal website is https://link.springer.com/journal/41030

The detailed author guidelines for Pulmonary Therapy are attached as Appendix 6.

Research publications in Pulmonary Therapy should have a structured abstract of 300 words or less, a plain language summary of 250 words or less, and a main text with no more than 4000 words (excluding acknowledgments, tables, figures and references).

Pulmonary Therapy requires line-numbering, but this has been omitted in this thesis, to preserve a uniform appearance throughout.

Pulmonary Therapy does not limit the number of tables, figures and references.

Pulmonary Therapy does not stipulate a font – the main text has been standardised to Times New Roman, 11 font size 11, 1.5 spacing. Figures and table titles have been standardised to Times New Roman font size 10**.** Table contents have been standardised to Times New Roman font size 9. Legends and abbreviations and foot notes have been standardised to Times New Roman font size 9 (italic).

AUTHOR CONTRIBUTIONS

Authorship

Dr Fefekazi Mpisane-Jama conceptualised, designed and wrote the protocol, conducted the study, set up the REDCap database, entered the data, was involved in data analysis / interpretation, and wrote, edited and finalised all drafts.

Wisdom Basera (a statistician collaborator) assisted with protocol design, extracted the data, and did the statistical analyses.

Professor Alan Horn supervised every aspect of the project from protocol development stage to final manuscript; he also reviewed and interpreted all the ultrasound images and edited all drafts of the protocol and manuscript.

All authors critically reviewed and approved the final manuscript.

ETHICAL APPROVAL

The study conformed to the principles of the 2013 Declaration of Helsinki [12] and was approved by the University of Cape Town Health Sciences Faculty Human Research Ethics Committee (No. 335/2022) (Appendix 4) and the management of Groote Schuur Hospital (Appendix 5). Data collection was complete before the expiry date of the approvals.

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Accumulating data suggest the potential for lung ultrasound (LUS) to diagnose lung pathology and predict the need for surfactant administration in preterm babies, but there are no published data from South Africa.

Objectives

The objectives were to describe LUS diagnoses and outcomes in preterm babies receiving non-invasive respiratory support in a South African neonatal unit, and to compare LUS with clinical diagnoses and surfactant administration.

Methods

We conducted a prospective, observational study of babies 27–34 weeks' gestation, birth weight ≥ 800 grams, receiving non-invasive respiratory support who had LUS at age ≤ 3 hours. Surfactant was administered at fraction of inspired oxygen (FiO_2) 0.35–0.45 and was not influenced by LUS findings.

Results

Over a 4-month period, 51 babies were included – eight (16%) received surfactant, all of whom had respiratory distress syndrome (RDS) as their only clinical diagnosis, compared to overlapping diagnoses in the non-surfactant group; RDS (93%), TTN (16%) and pneumonia (14%). Lung ultrasound suggested less RDS in the non-surfactant group (42% vs. 88%; p=0.002), and more TTN (79% vs. 38%; p=0.002) and TTN plus pneumonia (65% vs. 25%; p=0.03). The LUS score (LUSS) predicted surfactant administration (Area under the curve 0.8 [95% confidence interval 67-94%]). A LUSS of 7 had the best combined sensitivity (75%) and specificity (72%) but low positive predictive value (33%). A LUSS of 8 identified 8/43 (19%) additional babies for surfactant who did not need treatment.

Conclusion

Lung ultrasound suggested a higher frequency of alternative and additional diagnoses than clinical assessment but was not an adequate single indicator of surfactant requirement, compared to FiO_2 threshold. The high frequency of LUS features of TTN in the non-surfactant group, highlights the need to consider TTN as an alternative diagnosis in similar preterm neonates.

Key Words: *Neonate, newborn; Neonatal intensive care; Point-of-care ultrasound; lung ultrasound; respiratory distress syndrome; surfactant.*

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ABBREVIATIONS

AUC	Area under the curve
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
CRF	Case report form
CRP	C-reactive protein
CXR	Chest Xray/Radiograph
FiO2	Fraction of inspired oxygen
GA	Gestational age
GSH	Groote Schuur Hospital
HCU	High care unit
HFHNC	High flow humidified nasal canula
HMD	Hyaline membrane disease
INSURE	Intubation-surfactant-extubation
IQR	Inter quartile range
LISA	Less invasive surfactant administration
LR	Likelihood ratio
LUS	Lung ultrasound scan
LUSS	Lung ultrasound score
MAS	Meconium aspiration syndrome
nCPAP	Nasal Continuous Positive Airway Pressure
NEC	Necrotising enterocolitis
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NPV	Negative predictive value
PDA	Patent ductus arteriosus
PPV	Positive predictive value
PVIH	Periventricular intracranial haemorrhage
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROC	Receiver operating characteristics
ROM	Rupture of membranes
SD	Standard deviation
TTN	Transient tachypnoea of the new-born

CHAPTER 1: PUBLICATION-READY MANUSCRIPT

TITLE PAGE

Diagnostic Utility of Lung Ultrasound in Preterm Neonates with Respiratory Distress at a Tertiary Neonatal Intensive Care Unit in the Western Cape

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ABSTRACT

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Over a 4-month period, 51 babies were included – eight (16%) received surfactant, all of whom had (respiratory distress syndrome (RDS) as their only clinical diagnosis, compared to overlapping diagnoses in the non-surfactant group; RDS (93%), TTN (16%) and pneumonia (14%). Lung ultrasound suggested less RDS in the non-surfactant group (42% vs. 88%; p=0.002), and more TTN (79% vs. 38%; p=0.002) and TTN plus pneumonia (65% vs. 25%; p=0.03). The LUS score (LUSS) predicted surfactant administration (Area under the curve 0.8 [95% confidence interval 67-94%]). A LUSS of 7 had the best combined sensitivity (75%) and specificity (72%) but low positive predictive value (33%). A LUSS of 8 identified 8/43 (19%) additional babies for surfactant who did not need treatment.

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Key Words: *Neonate, newborn; Neonatal intensive care; Point-of-care ultrasound; lung ultrasound; respiratory distress syndrome; surfactant*

KEY SUMMARY POINTS

Why carry out this study?

- Respiratory distress syndrome (RDS) is a major contributor to the high neonatal mortality rates in low-income countries, but early treatment with surfactant can improve outcomes.

- There are accumulating data from high-income countries suggesting lung ultrasound (LUS) predicts earlier and more beneficial surfactant administration in preterm neonates with RDS, but there are few published data from lower- and middle-income countries, and no data from South Africa.

- This study described the use of LUS and explored the ability of a LUS score to predict surfactant administration in preterm neonates, treated with non-invasive ventilation in a tertiary South African neonatal unit.

What has been learned from this study?

- Lung ultrasound suggested significantly less RDS, more transient tachypnoea (TTN), and more TTN with pneumonia in the neonates who did not receive nor require surfactant, but LUS had lower predictive values (sensitivity 75%; specificity 72%; and positive predictive value 33%) for the administration of surfactant than other studies in both high- and middle-income countries.

- The higher frequency of TTN identified by LUS in the non-surfactant group, suggests it is underdiagnosed by clinical assessment, but the high frequency of pneumonia diagnosed by LUS, in this a low-risk group with a benign course, suggests that LUS over diagnosed pneumonia.

- Lung ultrasound was not sufficiently predictive of surfactant use in preterm neonates in the South African unit, where the administration threshold was fraction of inspired oxygen (FiO_2) of 0.35 – 0.45 and neonates who did not receive surfactant had a benign clinical course.

PLAIN LANGUAGE SUMMARY

Preterm babies may suffer from respiratory distress syndrome (RDS) due to immature lungs and surfactant deficiency. Surfactant can be administered as medication. Lung Ultrasound (LUS) can be done at the bedside and is increasingly used to evaluate lung disease and the need for surfactant, but there are no data from newborns in South Africa. We conducted an observational study to describe the use of LUS in preterm babies in South Africa. We included babies born at 27-34 weeks' gestation, birth weight of $\geq$ 800 grams, receiving non-invasive respiratory support, who had a LUS within 3 hours of birth.

Over a 4-month period, 51 babies were observed. Only 16% received surfactant, all of whom had RDS as their only diagnosis before LUS, compared to more variable and additional diagnoses in those who did not receive surfactant, including RDS (93%), transient tachypnoea of the newborn (TTN) due to fluid in the lungs in 16% and pneumonia (14%). Lung ultrasound added more detail than clinical diagnosis alone, suggesting proportionately less RDS in the non-surfactant group (42%), and more TTN (79%) and TTN with pneumonia (65%). The high incidence of TTN identified by LUS in the non-surfactant group, highlights TTN as being potentially under-diagnosed in this group.

The LUS score (LUSS) predicted surfactant administration, but not strongly, since it did not correctly predict surfactant in all babies and if used as the only indicator, it would have identified 19% additional babies who had an uneventful course without surfactant.

MAIN TEXT

INTRODUCTION

Respiratory distress syndrome (RDS) due to pulmonary surfactant deficiency is a major cause of death amongst preterm neonates, with a mortality rate of 40% to 60% in low-income countries – approximately ten times higher than in high-income countries. [1, 2] Early diagnosis and treatment are required for optimal outcome. A meta-analyses published over a decade ago, showed a significant reduction in the risk of neonatal mortality, and chronic lung disease (CLD) when surfactant is administered early to intubated neonates compared to delayed treatment. [3] More recently, optimal respiratory management to reduce bronchopulmonary dysplasia (BPD) and death includes early surfactant administration to neonates while treated with nasal continuous positive airway pressure (nCPAP). [1]

The diagnosis and severity of RDS, also known as hyaline membrane disease (HMD), is conventionally assigned based on increased oxygen requirement and respiratory distress in preterm neonates in the absence of other causes. While radiological features are typical, performing X-rays requires additional time, equipment, expertise and radiation exposure. [4] Lung ultrasound (LUS) is a non-invasive, quick and radiation-free bedside tool with the potential to diagnose neonatal lung pathologies including RDS, transient tachypnoea of the newborn (TTN), meconium aspiration syndrome (MAS), pneumothorax and pneumonia. [5-7] In addition, accumulating evidence suggests a role for LUS to predict surfactant requirement. [7-9]

Brat et. al. described a LUS score (LUSS) which correlated well with oxygenation status in neonates and predicted surfactant treatment; a LUSS > 4 was associated with an increase in the proportion of neonates with gestational age (GA) < 34 weeks requiring surfactant, from 25% to 75%. (8) A later prospective cohort study showed LUS scores of > 6 and > 8 had sensitivities and specificities of 90% and 80% vs. 82% and 92% respectively for predicting treatment with surfactant. [7] A more recent randomised controlled trial (RCT) comparing the use of a LUSS > 8 within the first 3 hours of life with an fraction of inspired oxygen (FiO_2) threshold of 0.3 – 0.4 as indications to administer surfactant, showed that the use of the LUSS was associated with earlier treatment at lower FiO_2. [9]

There are no published data or guidelines on the use of neonatal LUS in South Africa. At the time of this study, LUS was used at the discretion of the senior clinician as an additional diagnostic tool in Groote Schuur Hospital (GSH) neonatal intensive care unit (NICU) and high care unit (HCU), but early LUS in the first three hours was encouraged, in keeping with the practice in some neonatal units in other countries. [10, 11]

This study was designed to address the knowledge gap of South African experience with neonatal LUS, by describing the experience and clinical utility of early LUS in preterm neonates treated with nasal CPAP (nCPAP) or high flow humidified nasal canula (HFHNC) in a public, tertiary neonatal unit in South Africa. The primary objective was to describe the early LUS findings, respiratory pathologies, associated major morbidities and mortality in a cohort of preterm neonates < 34 weeks GA, treated with nCPAP or HFHNC, who were surfactant-naïve at the time of LUS. The secondary objectives were to compare LUS findings with clinical diagnoses and describe the association between LUSS and surfactant administration.

METHODS

Study design and population

We carried out an exploratory, prospective, observational cohort study of preterm neonates admitted to the GSH NICU and HCU who were treated with nCPAP or HFHNC and had early LUS during a four-month period – a convenience period based on feasibility of prospective data collection. The GSH neonatal unit has approximately 2 000 admissions per annum and is the major tertiary referral centre for the Metro West Area of Cape Town.

The study conformed to the principles of the 2013 Declaration of Helsinki [12] and was approved by the University of Cape Town Health Sciences Faculty Human Research Ethics Committee (No. 335/2022) and the management of GSH.

Inclusion and exclusion criteria

The inclusion criteria were selected to identify preterm neonates with suspected RDS, who were eligible for intubation and surfactant administration according to provincial guidelines. These included: inborn neonates admitted to GSH neonatal unit; 27 to 34 weeks GA at birth; birth weight ≥ 800 grams (g); respiratory support at the time of recruitment with nCPAP or HFHNC; and LUS at age ≤ 3 hours. Neonates with any of the following exclusion criteria were not recruited: received surfactant before LUS; congenital/chromosomal abnormalities; or intubated after meeting entry criteria but prior to LUS.

Standard care and gestational age assessment

All aspects of clinical management were according to existing standard hospital protocols and were the same irrespective of recruitment. Gestational age assessment was based on early obstetric ultrasound scan (EUS) if performed < 20 weeks GA or, in the absence of an early scan, the Ballard score was used if birth weight was ≥ 1000 g, [13] and measurement of foot length using Vernier callipers was used when birth weight was < 1000 g. [14] Infants with infection risk factors at any stage during their admission were investigated and treated according to the 2021 National Institute for Health and Care Excellence (NICE) guidelines. [15] Antibiotics were stopped after 36-48 hours if C-reactive protein (CRP) was < 10 mg/dl and the blood culture was negative.

Respiratory management

Respiratory management was based on the 2019 European guidelines. [1] Neonates with respiratory distress after birth who did not require intubation were commenced on mask CPAP, transferred to the NICU, and placed on nCPAP at 5-7 cm water. Surfactant was not given in the delivery room. Oxygen saturation was monitored continuously and FiO_2 adjusted to maintain pre-ductal saturation at 90-95%. If the FiO_2 was persistently > 0.35-0.45, surfactant was administered. At the time of the study, Survanta® was the only surfactant in use, at a dose of 4 ml/kg (100 mg/kg) via the less invasive surfactant administration (LISA) or intubation-surfactant-extubation (INSURE) methods. [1] A Chest X-Ray (CXR) was not routinely performed prior to surfactant administration via LISA or INSURE. Repeat dosing was considered if FiO_2 remained above 0.45 after 6-12 hours. Indications for intubation and mechanical ventilation included apnoea, persistent hypotension requiring inotropes, and respiratory acidosis with pH < 7.25 and / or FiO_2 > 0.6 after surfactant.

Recruitment and informed consent

Infants meeting inclusion criteria were identified by daily review of admissions of all preterm newborns admitted to the GSH NICU and HCU who were treated with nCPAP or HFHNC, by a research clinician (FM) during normal attending hours from August to November 2022. Lung ultrasound was done in discussion with the attending clinician. The LUS findings were not used to influence the decision to administer surfactant, but if any life-threatening abnormalities such as pneumothorax were observed on ultrasound, these would be confirmed clinically and treated. After obtaining informed consent from the mother or guardian, the maternal and infant demographic data; maternal medical and obstetric history; labour and delivery data; clinical details of the infant at birth; diagnoses during admission; interventions and treatment; lung ultrasound findings and outcome data were entered into a case record form (CRF).

Lung ultrasound procedures

For the duration of the study, LUS was performed by a single clinician (FM), with training in LUS, using a Vivid-IQ (GE Healthcare, USA) ultrasound scanner with a wideband linear array probe (4-15 MHz) as described by Brat et al.[8] The thorax was scanned in three areas per hemi-thorax – an anterior area defined by parasternal and anterior axillary lines, a lateral area defined by anterior and posterior axillary lines, and a posterior area defined by the posterior axillary line; transverse and longitudinal images were recorded for each area. [8] Lung ultrasound images were exported under the study number to an external hard drive for later blinded assessment by researcher AH.

Ultrasonographic findings were described based on standard definitions: lung sliding – movement between lung and pleura; A-lines – artifacts resulting from reflections of the pleura; B-lines - artifacts created by reflections of fluid in the lungs; and Pleural lines – echogenic lines formed by the chest wall soft tissues and the aerated lung interface. A LUSS was derived by allocating a score of 0 - 3 to each lung area, as follows: A-pattern (visualisation of A-lines only), score = 0; B-pattern (≥ 3 well-spaced B-lines), score =1; Severe B-pattern (crowded and coalescent B-lines with or without consolidation confined to the subpleural space), score = 2; and extended consolidations, score = 3. A total score was calculated by adding the individual scores from each lung zone to a maximum score of 0 to 18. [8, 16]

The LUS was also assessed and scored for features of TTN, pneumonia and pneumothorax, with each feature assigned a score of one. Features of TTN in this study included one or more of: A double lung point (defined as two patterns seen in one view including normal A-pattern/B-pattern or B/severe B pattern); a gradient of echogenicity between inferior and superior areas with lower echogenicity in superior areas, including areas with non-compact B-lines and but no area with extended consolidation; or a LUSS of 1 – 6 with normal lung / non-compact B-lines. [6, 17, 18] Features of pneumonia in this study included one or more of: Absent lung sliding together with any B-lines present in same view; absent lung sliding, absent B-lines but lung pulse present and no lung point in same view; LUSS < 6 with pleural line abnormalities (disappearance / irregularity / coarse) or any lung consolidation/air bronchograms; large (> 1cm) areas of lung consolidation with irregular margins without a B/severe B pattern. [19] A pneumothorax was diagnosed by the presence of a lung point - the transition point between an area of lung sliding and absence of lung sliding and absent B-lines, or absent lung pulse without B-lines or lung pulse. [19, 20] A LUS respiratory diagnosis was assigned – these data were entered into a separate LUS report form.

Data management

The data from the CRF and the LUS report form were de-identified and entered into a UCT-hosted REDCap data base. A list of patients' identifying data was kept separately in a password-protected computer accessible only to the clinician researchers. A convenience, time-based sample was used; researchers anticipated that approximately 50 neonates would be recruited during the four-month study period. A power calculation was not performed since this study was exploratory and descriptive and aimed to obtain baseline data to inform further studies. Demographic, clinical, outcome and lung ultrasound data were presented using descriptive statistics depending on data normality. Stata Version 15 (Stata Corporation; College Station, USA, 2017) was used for statistical analysis. Data were grouped according to surfactant treatment. The Chi square or Fisher's exact tests were used for categorical comparisons, depending on the expected values. The Student's t-test or Wilcoxon-Mann-Whitney rank sum tests were used for comparison of parametric and non-parametric continuous variables respectively, depending on data normality.

Receiver operating characteristic (ROC) analysis was used to evaluate the ability of the LUSS to predict surfactant administration; area under the curve (AUC) and cut-off values showing sensitivity, specificity, predictive values, and likelihood ratios (LR) were reported. A logistic regression model was used to predict the probability of surfactant administration for every unit increase in the LUSS. Statistical significance was denoted by a p-value of < 0.05.

RESULTS

Recruitment and baseline characteristics

The recruitment flow and management of included neonates is shown in figure 1. After exclusion of 72 neonates, 51 of the 123 potentially eligible neonates were included, eight (16%) of whom received surfactant after failing nCPAP. The baseline characteristics of the cohort, grouped according to surfactant administration are shown in table 1. There were no differences in antenatal factors, labour, and delivery characteristics between groups. Maternal hypertension was the most frequent antenatal diagnosis (43%), and the majority of mothers received antenatal care (94%) and antenatal steroids (90%). Abnormal intrapartum events occurred in 50% and most neonates (92%) were delivered by caesarean section. However, risk factors for infection were infrequent; spontaneous labour (33%), prelabour rupture of membranes (ROM) (18%), prolonged ROM (6%) and no mother received intrapartum antibiotics. Approximately half (53%) of the neonates were male. The birth weights and gestational ages were lower in the surfactant group (median weight 1178 g vs 1612 g; p=0.02 and median GA 29 vs. 32 weeks; p=0.05). Only 33% had an early blood gas however there were no differences in resuscitation at birth and admission temperature between groups.

Respiratory characteristics, pathologies and lung ultrasound features

The respiratory characteristics, pathologies and lung ultrasound features are shown in Table 2. There were no significant differences in diagnoses between treatment groups based on clinical assessment without LUS, however TTN and pneumonia were not diagnosed clinically in the surfactant group, compared to 16% and 14% respectively in the non-surfactant group. In contrast, the diagnoses based on LUS indicated a higher relative proportion of RDS in the surfactant group (88% vs. 42%; p=0.002), and fewer neonates with TTN (38% vs. 79%; p=0.002) and TTN with pneumonia (25% vs. 65%; p=0.03). At the time of the LUS, the FiO_2 was more frequently lower in neonates who did not receive surfactant ($FiO_2 < 0.35$ in 50% vs. 84% of surfactant group; p=0.03). The FiO_2 increased to 0.45 during the scan in one neonate who received surfactant immediately after the scan.

There were no statistically significant differences in the type of respiratory support between the two groups. However, none of the infants on HFNC required surfactant. The neonates who received surfactant had higher mean LUS scores (7.5 ±1.6 vs. 5.0 ±2.4; p=0.01) and lower mean TTN scores (0.75±1.16 vs. 1.74±1.16; p=0.03) compared to the non-surfactant group. The differences between clinical and LUS diagnosis for the cohort overall are further summarised in table 3. The diagnoses by clinical assessment alone compared with LUS, showed a higher proportion of RDS (94% vs. 49% with LUS; p<0.001), and lower proportions of TTN (14% vs.73%; p<0.001) and pneumonia (12% vs. 71%; p<0.001) and combinations including TTN and pneumonia. The detailed individual lung ultrasound findings are shown in table 4; there were no differences between groups.

Lung ultrasound score prediction model

The receiver operating characteristic (ROC) curve for the LUSS to predict administration of surfactant is shown in figure 2. Logistic regression analysis showed that the area under the curve (AUC) was 0.8 (95% confidence interval (CI): 0.67-0.94) with adequate fit and acceptable discrimination for the model (Hosmer & Lemeshow p=0.92). The LUSS was a significant predictor of surfactant administration with an increasing odds ratio (OR) for every 1-unit increase in LUSS of 1.68 (CI: 1.10-2.57), p=0.02.

The sensitivity, specificity, predictive values and LR at different LUS scores are shown in table 5. The LUSS of ≥ 6 had a high negative predictive value (NPV) (96%), but only a 14% probability of surfactant administration. The LUSS giving the correct classification (73%) with highest sensitivity (75%) was a LUSS of 7, which coincided with the probability cut-off of 21% at the intersection of positive predictive value (PPV) and negative predictive value (NPV) (figure 3). However, at this value the PPV (33%) and specificity (72%) were low. A LUSS ≥ 10 was associated with high specificity (98%), increased correct classification (84%) and highest positive LR (5.4), but sensitivity (13%) was very low.

Morbidity and mortality

The morbidity and mortality, grouped according to surfactant treatment is shown in table 6. The mean maximum FiO_2 was higher in the group who received surfactant (0.57±0.2 vs 0.29±0.06; p=0.01). The only neonate who required intubation for ventilation in the first week was in the surfactant group and duration of any respiratory support was longer in the surfactant group (median days [IQR]: 8 [4.5-13] vs. 3 [2-6]; p=0.01). The surfactant group had higher maximum CRP values (median [IQR]: 10 [1-39] vs. 1 [1-2]; p=0.02), more necrotising enterocolitis (NEC) (25% vs 0; p=0.01); and more blood transfusions (38% vs. 2%; p=0.01). Only one neonate in the cohort developed BPD and there was one death in the cohort, which was in the non-surfactant group, due to gram-negative septicaemia.

DISCUSSION

This study of early LUS in surfactant-naïve neonates at 27-34 weeks GA, during non-invasive ventilation, found that LUS suggested a wider range of diagnoses than clinical assessment alone and it predicted surfactant administration, but the PPV for the LUSS was low and only 16% of the cohort required surfactant.

The LUSS of 7 in our study, had the most appropriate combined sensitivity (75%) and specificity (72%) but a low PPV (33%). A LUSS of 8 was suggested as the most appropriate predictive score in the cohort study by De Martino et al.; the predictive values were high (sensitivity 82%, specificity 92% and PPV 92%) however their cohort only included neonates ≤ 30 weeks GA, and their threshold FiO_2 for surfactant administration was > 0.3 or > 0.4 for

neonates ≤ 28 and > 28 weeks GA, respectively. [7] The LUSS threshold of 8 was subsequently compared to the same FiO2 thresholds as De Martino et al. in a RCT including neonates < 32 weeks GA. (9) The LUSS of 8 was associated with earlier treatment than FiO_2 thresholds (Age 1 h vs. 6 h, $p < 0.001$), at lower FiO_2 (0.25 vs. 0.3, $p = 0.016$) and a greater SpO_2/FiO_2 ratio after treatment. [9] Importantly, both these studies had lower inclusion GA limits and lower FiO_2 administration thresholds than our study, and both were in high-income countries. In contrast to their findings, the LUSS of 8 in our study had lower sensitivity (50%) and PPV (33%); although the specificity was high (81%), the use of this score would have indicated surfactant treatment in 8 (19%) additional neonates, none of whom ultimately required or received surfactant.

Our findings also differ from a recent observational study in India. [21] Singh et al. enrolled 100 neonates < 34 weeks GA, similar to our study, but surfactant administration at FiO_2 of 0.3 was lower than our study with more frequent surfactant administration (40% vs. 16%), and age at LUS was earlier than our study (mean 1.37 vs median 2.1 hours). [21] Although a LUSS of 7 was the best predictor of surfactant administration in their study, they reported much higher predictive values (sensitivity 92.5%, specificity 96.7%, and PPV 94.9%).

The benefit of LUS in identifying alternative diagnoses to RDS and the high concordance with CXR and interobserver agreement is well described. [10, 11] In keeping with those findings, our study demonstrated that LUS more frequently indicated diagnoses other than RDS compared to clinical assessment alone, particularly in the non-surfactant group (TTN: 79% vs 16% clinical assessment and pneumonia: 74% vs. 14% clinical assessment). Individual LUS diagnostic features for both TTN and neonatal pneumonia have been established, but there remains significant variability in predictive values of individual and collective features between studies, and there is considerable overlap between the LUS features. [22]

While several studies show high diagnostic sensitivity and specificity of features of TTN, these studies frequently included term and/or near-term neonates, late presentations, ventilated neonates and/or asymptomatic controls. [23] The TTN score we developed, awarded cumulative points for each feature of TTN; a score of ≥ 2 occurred in 61% of neonates in the non-surfactant group compared to 13% of the surfactant group – it may be a more robust diagnostic indicator of TTN, but this should be evaluated further in larger samples. Despite these limitations, the increased diagnosis of TTN in the non-surfactant group of our study was in keeping with their benign clinical course (median 3 days respiratory support with no intubation).

The five-times higher frequency of LUS features of pneumonia compared to clinical diagnoses in our study, and the frequent co-existence with TTN, needs further consideration. Our assignment of diagnoses based on “any” features being present, rather than a collection of features, highlights this conundrum. The low frequency of sepsis indicators (< 16% pre-labour/prolonged ruptured membranes, no chorioamnionitis, no intrapartum antibiotics, and median highest CRP 1 mg/dl), in the non-surfactant group suggests that the 74% frequency of pneumonia represented substantial over-diagnosis by LUS. Liu et al. reported that a large area of lung consolidation with irregular margins on LUS, had 100% sensitivity and specificity for the diagnosis of neonatal pneumonia. [24] However, their study was based on a non-consecutive convenience sample of neonates with suspected pneumonia, compared to a control group admitted for non-pulmonary reasons.

Our sample was not designed to establish diagnostic criteria for pneumonia as it contained a group at low risk for pneumonia. It is therefore not surprising that we did not find a difference between surfactant treated and untreated groups in any of the features for pneumonia including, consolidation with irregular margins, absent lung sliding with

B-lines in the same view, absent lung sliding, absent B-lines but presence of lung pulse and absent lung point in the same view. However, the high frequency of features indicating pneumonia in a setting where pulmonary infection was highly unlikely, indicate the need for caution when interpreting LUS findings.

The increased morbidity in the surfactant-treated group in our study was probably related to the associated lower birth weight and lower GA in this group. Although early vs. delayed surfactant administration is associated with decreased morbidity and mortality in intubated neonates, [3] the additional intervention of surfactant administration to neonates receiving nCPAP, may contribute to morbidity if it is not indicated. The benign course of the untreated neonates suggests that surfactant was not indicated. The low overall morbidities, particularly sepsis (2%) and NEC (4%), and the low mortality rate of 1.9% in our cohort relative to the higher rates reported in both high- and low-income countries, suggests that our management protocols and intervention thresholds are reasonable. [1, 2] If a LUSS of 7 was used instead of the FiO_2 threshold of 0.35 – 0.45, 25% (2/8) of the neonates who received surfactant would not have been treated, which may have led to more intensive later intervention, and 28% (12/43) of those who did not receive surfactant, would have been treated, with potential increased morbidity associated with the intervention.

Limitations and strengths

This study has several limitations. First, the sample size was small, exploratory and limited by time and availability of the clinician performing the LUS. Second, the study included some neonates receiving HFNC, and LUS may appear different with HFNC compared to nCPAP, however the majority (86%) were receiving nCPAP. Third the inclusion of neonates > 32 weeks' GA led to sample with a low requirement of surfactant. Despite these limitations, this study is the first to contribute novel neonatal LUS data from a South African centre, which may be used to inform the design of future studies. The collection of data at a single centre by one clinician performing the LUS scans, may provide more uniform data, and the interpretation of the scans by a second clinician who was blinded to the clinical data at the time of review, may have decreased bias.

CONCLUSION

Early LUS in this study of surfactant-naïve preterm neonates, identified a wider range of diagnoses than clinical assessment alone, but the predictive values of LUS scores for surfactant administration at the FiO_2 thresholds in use at our institution, were low. The high frequency of features of TTN in the non-surfactant group, and the associated benign clinical course, highlights TTN as an alternative diagnosis in similar preterm neonates. However, larger prospective studies are needed to establish optimal criteria to diagnose TTN and pneumonia, using more robust diagnostic scores including features of TTN and pneumonia in neonates with clinical diagnostic uncertainty.

Our findings do not preclude the potential predictive value of the LUSS for surfactant administration, where inclusion GA is limited to ≤ 32 weeks and/or if lower FiO2 thresholds for surfactant administration are used. However, further larger, gestation-stratified studies of the LUSS in similar settings are needed, before routinely replacing, or supplementing the FiO_2 threshold with LUSS in our setting.

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Ethics/Ethical Approval

The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments including the principles of the 2013 Declaration of Helsinki.

The study and was approved by the University of Cape Town Health Sciences Faculty Human Research Ethics Committee (No. 335/2022) and the management of Groote Schuur Hospital.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Clinician/Patient involvement

I would like to thank the Department of Neonatology at Groote Schuur Hospital, the nurses, and the doctors (junior and senior) who have contributed to the care of these patients. Although they did not contribute to this manuscript, their involvement in the care of the patients is acknowledged.

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TABLES

Table 1: Baseline Characteristics

Variable	Whole Cohort N=51	No Surfactant n=43	Received Surfactant n=8	P value
ANTENATAL FACTORS				
Antenatal care, n (%)	47 (94)	39 (93)	8 (100)	1.00 [a]
Maternal illicit drug use/alcohol/smoking, n (%)	4 (8)	4 (9)	0	1.00 [a]
Maternal hypertension, n (%)	22 (43)	19 (44)	3 (38)	1.00 [a]
Antenatal or Intrapartum $MgSO_4$, n (%)	16 (31)	13 (30)	3 (38)	0.69 [a]
Diabetes, n (%)	0	0	0	-
Antenatal pyrexial illness/ infection/ antibiotics, n (%)	1 (2)	0	1 (13)	0.16 [a]
Antenatal Steroids, n (%)	46 (90)	38 (88)	8 (100)	0.58 [a]
Two doses antenatal steroids, n (%)	29/46 (63)	25/38 (66)	4/8 (50)	0.71 [a]
Days between antenatal steroids last dose and delivery, n(%)				
< One	10/46 (22)	7/38 (18)	3/8 (37)	0.23
> Seven	14/46 (30)	11/38 (29)	3/8 (37)	0.63
LABOUR and DELIVERY				
Spontaneous preterm labour, n (%)	17 (33)	13 (30)	4 (50)	0.42 [a]
Caesarean delivery, n (%)	47 (92)	40 (93)	7 (88)	0.51 [a]
Prelabour ROM, n (%)	9 (18)	7 (16)	2 (25)	0.62 [a]
Prolonged ROM > 18 h, n (%)	3 (6)	3 (7)	0	1.00 [a]
Clinical Chorioamnionitis/ Intrapartum antibiotics, n (%)	0	0	0	-
Abnormal intrapartum events, n (%)	22 (43)	18 (42)	4 (50)	0.71 [a]
NEONATAL DETAILS				
Male, n (%)	27 (53)	25 (58)	2 (25)	0.13 [a]
Birthweight (grams), mean (SD)	1544 (±481)	1612 (±484)	1178 (±261)	***0.02*** [c]
Gestation at birth (weeks), med (IQR) n_1=50; n_2=42; n_3=8	32 (29-34)	32 (29-34)	29 (28-31)	***0.05*** [b]
5-minute Apgar score, med (IQR)	9 (7-9)	9 (7-9)	9 (8.5-9.0)	0.57 [b]
Cord/infant blood gas done within the 1st hour of birth, n (%)	16 (31)	14 (33)	2 (25)	1.00 [a]
Temperature at 1 hour, mean (SD) n_1=50; n_2=42; n_3=8	36.18 (±0.44)	36.16 (±0.47)	36.25 (±0.30)	0.61 [c]

[a] *Fisher's exact test;* [b] *Wilcoxon-Mann-Whitney test;* [c] *Student t-test*
IQR - inter quartile range; ROM - rupture of membranes; SD - standard deviation.

Table 2: Respiratory characteristics and lung ultrasound scores

Variable	Whole Cohort N=51	No Surfactant n=43	Received Surfactant n=8	P value
Clinical respiratory diagnosis (without LUS), n (%):				
RDS	48 (94)	40 (93)	8 (100)	0.44 [a]
Pneumonia	6 (12)	6 (14)	0	0.26 [a]
TTN	7 (14)	7 (16)	0	0.22 [a]
Pneumothorax	0	0	0	-
Age at lung scan (hours), med (IQR)	2.1 (1.4-2.6)	2.1 (1.5-2.6)	1.5 (1.1-2.5	0.24 ‡
Fio2 at scan, med (IQR)	0.3 (0.2-0.3)	0.3 (0.2-0.3)	0.4 (0.3-0.4)	***0.01*** ‡
Fio2 at scan				
<0.35	40 (78)	36 (84)	4 (50)	***0.03*** [a]
0.35-0.44	10 (20)	7 (16)	3 (37)	0.17
≥0.45	1 (2)	0	1 (13)	***0.02***
Respiratory support at scan, n (%)				
nCPAP	44 (86)	36 (84)	8 (100)	0.22
HFNC	7 (14)	7 (16)	0	0.22 [a]
LUS score, median (IQR)	5.0 (4.0-7.0)	5.0 (3.0-7.0)	7.5 (6.5-8.5)	***0.01*** [b]
TTN score, median (range)	2 (0-3)	2 (0-3)	0.5 (0-3)	***0.04*** [b]
Pneumonia Score, med (range)	1.0 (0-4.0)	1.0 (0-4.0)	0.5 (0-1.0)	0.23 [b]
Respiratory diagnosis on LUS, n (%):				
RDS (LUSS ≥ 6)	25 (49)	18 (42)	7 (88)	***0.02*** [a]
TTN (LUS: any features)	37 (73)	34 (79)	3 (38)	***0.02*** [a]
Pneumonia (LUS: any features)	36 (71)	32 (74)	4 (50)	0.16 [a]
RDS plus TTN	11 (22)	9 (21)	2 (25)	0.80
RDS plus Pneumonia	11 (22)	8 (19)	3 (38)	0.23
TTN plus Pneumonia	30 (59)	28 (65)	2 (25)	***0.03***
RDS plus pneumonia plus TTN	5 (10)	4 (9)	1 (13)	0.78
Pneumothorax	0	0	0	-

[a] *Fisher's exact test;* [b] *Wilcoxon-Mann-Whitney test*

IQR-inter quartile range; LUS-lung ultrasound; LUSS-lung ultrasound score; RDS- respiratory distress syndrome; TTN-transient tachypnoea of the new-born.

Table 3: Respiratory diagnoses by clinical and lung ultrasound assessment

Variable (diagnosis)	Clinical diagnosis N=51	Diagnosis according to LUS N=51	p-value
RDS (LUSS ≥ 6)	48 (94)	25 (49)	***<0.001***
TTN (LUSS: any features)	7 (14)	37 (73)	***<0.001***
Pneumonia (LUSS: any features)	6 (12)	36 (71)	***<0.001***
RDS and TTN	4 (8)	11 (22)	***0.05***
RDS plus Pneumonia	6 (12)	11 (22)	0.18
TTN plus Pneumonia	0	30 (59)	***<0.001***
RDS plus pneumonia plus TTN	0	5 (10)	***0.02***
Pneumothorax	0	0	-

LUSS-lung ultrasound score; RDS- respiratory distress syndrome;
TTN-transient tachypnoea of the new-born

Table 4: Detailed individual lung ultrasound findings

Variable	Whole Cohort N=51	No Surfactant n=43	Received Surfactant n=8	P value
B-pattern (anywhere), n (%)	49 (96)	41 (95)	8 (100)	0.53 [a]
Severe B-pattern (anywhere), n (%)	22 (43)	16 (37)	6 (75)	***0.05*** [a]
Double lung point, n (%)	23 (45)	21 (49)	2 (25)	0.21 [a]
LUSS, n (%)				
Zero	1 (2)	1 (2)	0	0.36 [a]
One	2 (4)	2 (5)	0	
Two	3 (6)	3 (7)	0	
Three	6 (12)	6 (14)	0	
Four	6 (12)	6 (14)	0	
Five	9 (18)	8 (19)	1 (13)	
Six	6 (12)	5 (12)	1 (13)	
Seven	6 (12)	4 (9)	2 (25)	
Eight	8 (16)	6 (14)	2 (25)	
Nine	2 (4)	1 (2)	1 (13)	
Ten	1 (2)	0	1 (13)	
Eleven	1 (2)	1 (2)	0	
Gradient of echogenicity present, n (%)	31 (61)	28 (65)	3 (38)	0.24 [a]
TTN score, n (%)				
Zero	13 (25)	9 (21)	4 (50)	0.08
One	11 (22)	8 (19)	3 (38)	
Two	11 (22)	11 (26)	0	
Three	16 (31)	15 (35)	1 (13)	
Absent lung sliding and B-lines present in same view, n (%)	13 (25)	12 (28)	1 (13)	0.36 [a]
Absent lung sliding, absent B-lines, absent lung point, Lung pulse present, n (%)	1 (2)	1 (2)	0	0.66 [a]
LUSS < 6 with pleural abnormalities or lung consolidation, n (%)	22 (43)	20 (47)	2 (25)	0.26 [a]
Large irregular lung consolidation without B/Severe B, n (%)	6 (12)	5 (12)	1 (13)	0.94 [a]
Pneumonia Score, n (%)				
Zero	15 (29)	11 (26)	4 (50)	0.16
One	32 (63)	28 (65)	4 (50)	0.42
Two	3 (6)	3 (7)	0	0.44
Three	0	0	0	-
Four	1 (2)	1 (2)	0	0.66

[a] *Fisher's exact test.* *LUSS-lung ultrasound score; TTN-transient tachypnoea of the newborn*

Table 5: Predictive values at individual cut off values of LUSS on ROC curve to predict surfactant.

LUSS Cut off	Probability of surfactant administration [a]	Sensitivity [b]	Specificity [c]	PPV [d]	NPV [e]	Correctly classified [f]	LR+	LR-
≥0	≥0.0069	100%	0%	15.69%	0%	15.69%	1.0000	
≥1	≥0.0111	100%	2.33%	16.00%	100%	17.65%	1.0238	0.0000
≥2	≥0.0192	100%	6.98%	16.67%	100%	21.57%	1.0750	0.0000
≥3	≥0.0322	100%	13.95%	17.78%	100%	27.45%	1.1622	0.0000
≥4	≥0.0528	100%	27.91%	20.51%	100%	39.22%	1.3871	0.0000
≥5	≥0.0857	100%	41.86%	24.24%	100%	50.98%	1.7200	0.0000
≥6	≥0.1361	87.50%	60.47%	29.17%	96.30%	64.71%	2.2132	0.2067
≥7	≥0.2091	75.00%	72.09%	33.33%	93.94%	72.55%	2.6875	0.3468
≥8	≥0.3083	50.00%	81.40%	33.33%	89.74%	76.47%	2.6875	0.6143
≥9	≥0.4279	25.00%	95.35%	50.00%	87.23%	84.31%	5.3750	0.7866
≥10	≥0.5572	12.50%	97.67%	50.00%	85.71%	84.31%	5.3750	0.8958
≥11	≥0.6787	0%	97.67%	0	84.00%	82.35%	0.0000	1.0238
>11	≥0.6788	0%	100%	0	84.31%	84.31%		1.0000

[a]Was estimated using the logistic regression model that was fitted.
[b]Proportion of participants who received surfactant who were detected using this cutoff.
[c]Proportion of participants who received surfactant who were detected using this cutoff.
[d]Proportion of those detected as receiving surfactant using this cutoff that truly had it applied.
[e]Proportion of those who were not detected as not receiving surfactant using this cutoff that truly did not have it applied.
[f]Overall proportion of positives and negatives that were correctly classified. Note that this proportion is always biased toward the larger group.
LUSS – Lung ultrasound score; LR - likelihood ratio; NPV – negative predictive value; PPV – positive predictive value;
ROC- Receiver operating characteristics

TABLE 6: Morbidity and mortality

Variable	Whole Cohort N=51	No Surfactant n=43	Received Surfactant n=8	P value
LUS score, median (IQR)	5.0 (4.0-7.0)	5.0 (3.0-7.0)	7.5 (6.5-8.5)	***0.01*** [a]
Highest FiO2 first 24 h, mean (SD)	0.34 (0.14)	0.29 (0.06)	0.57 (0.20)	***0.01***
Surfactant doses, n (%)				
One	6 (12)	0	6 (75)	***<0.001***
Two	2 (4)	0	2 (25)	***<0.001***
Days intubated in first week, median (range)	0 (0-6)	0 (0)	0 (0-6)	0.31
Days of any respiratory support, median (IQR)	3.5 (2-7)	3.0 (2-6)	8 (4.5-13)	***0.01***
BPD, n (%)	1 (2)	1 (2)	0	0.66
Inotropes, n (%)	0	0	0	-
Surgery/treatment for PDA, n (%)	0	0	0	-
Early bacterial infection, n (%)	0	0	0	-
Late bacterial infection, n (%)	1 (2)	1 (2)	0	0.66
Highest CRP (mg/dl), med (IQR)	1 (1-3)	1 (1-2)	10 (1-39)	***0.02***
NEC (Bell stage 2 or 3), n (%)	2 (4)	0	2 (25)	***<0.01***
Blood transfusion, n (%)	4 (8)	1 (2)	3 (38)	***<0.01***
Severe PVIH (grade 3 or 4) , n (%)	0	0	0	-
Severe PVL (grade 3 or 4) , n (%)	0	0	0	-
Hypoglycaemia, n (%)	0	0	0	-
Hyponatraemia, n (%)	0	0	0	-
Metabolic Bone Disease, n (%)	6 (12)	4 (9)	2 (25)	0.21
Formula milk (any) , n (%)	46 (90)	39 (91)	7 (88)	0.78
Mortality, n (%)	1 (2)	1 (2)	0	0.66

[a] *Wilcoxon-Mann-Whitney test; BPD-broncho-pulmonary dysplasia; IQR-inter quartile range; LUSS –lung ultrasound score; NEC-necrotising enterocolitis; PDA-patent ductus arteriosus; PVIH-periventricular intracranial haemorrhage; PVL-periventricular leukomalacia; SD-standard deviation.*

FIGURE LEGENDS

Figure 1: Recruitment flow and management of included babies.
HFHNC – high flow humified nasal canula; LUS – lung ultrasound;
nCPAP – nasal continuous positive airway pressure

Figure 2: Receiver Operating Characteristics curve for LUS score to predict surfactant administration.
LUS – lung ultrasound scan; ROC – receiver operating characteristics

Figure 3. Intersection of PPV and NPV of LUS score to predict surfactant administration.
LUS – lung ultrasound scan; NPV – negative predictive value; PPV – positive predictive value

FIGURES

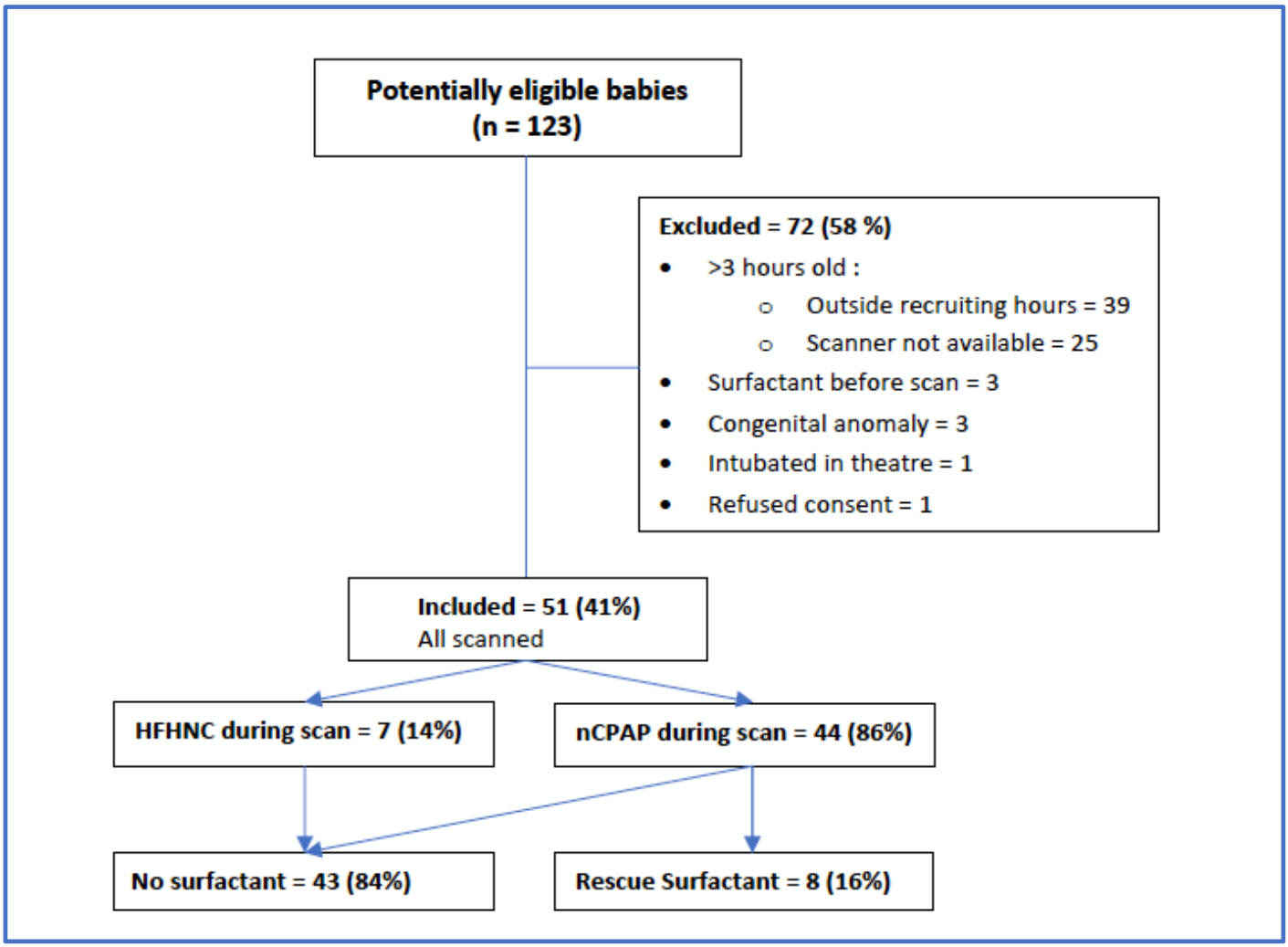

Figure 1: Recruitment flow and management of included babies.
HFHNC – high flow humified nasal canula; LUS – lung ultrasound scan;
nCPAP – nasal continuous positive airway pressure

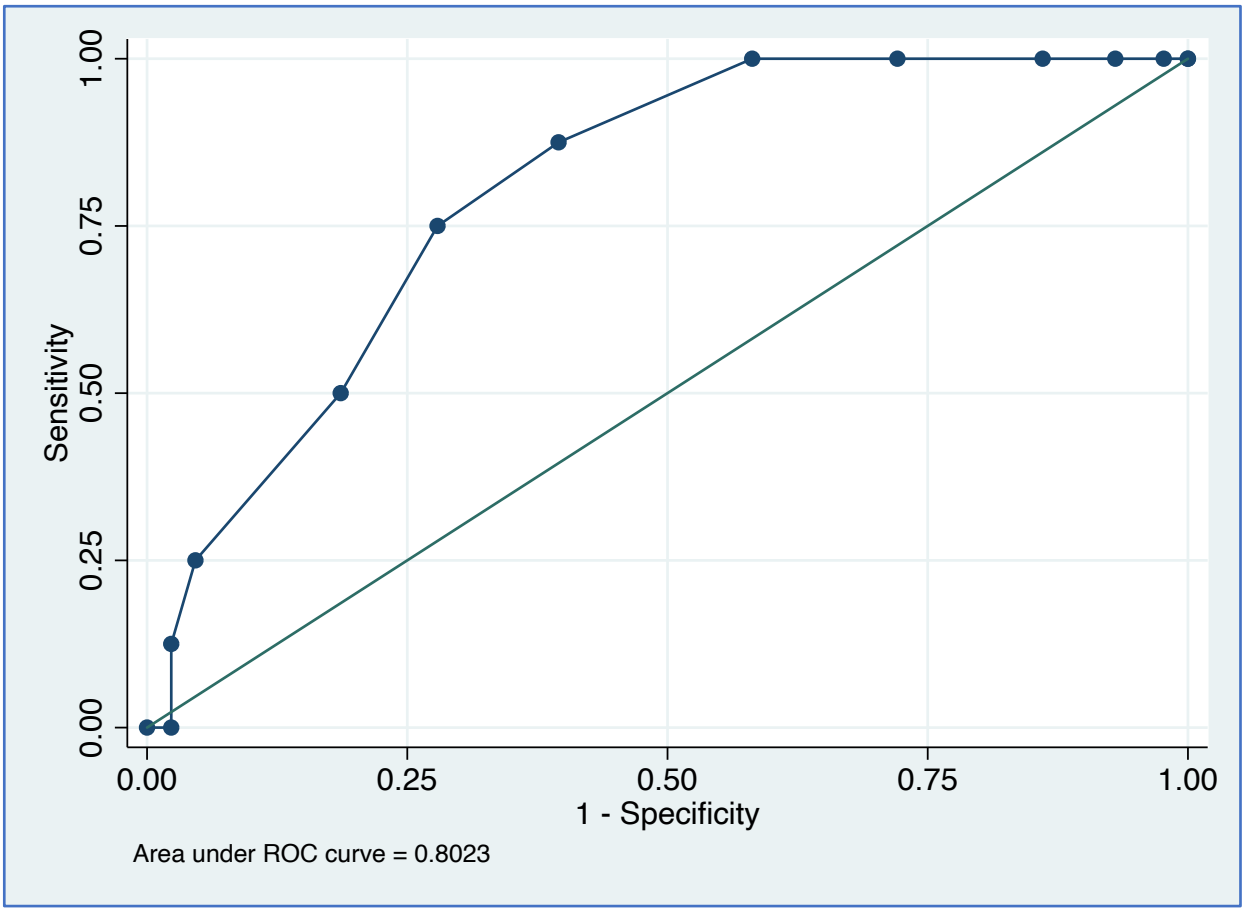

Figure 2: Receiver Operating Characteristics curve for LUS score to predict surfactant administration
LUS – lung ultrasound scan; ROC – receiver operating characteristics

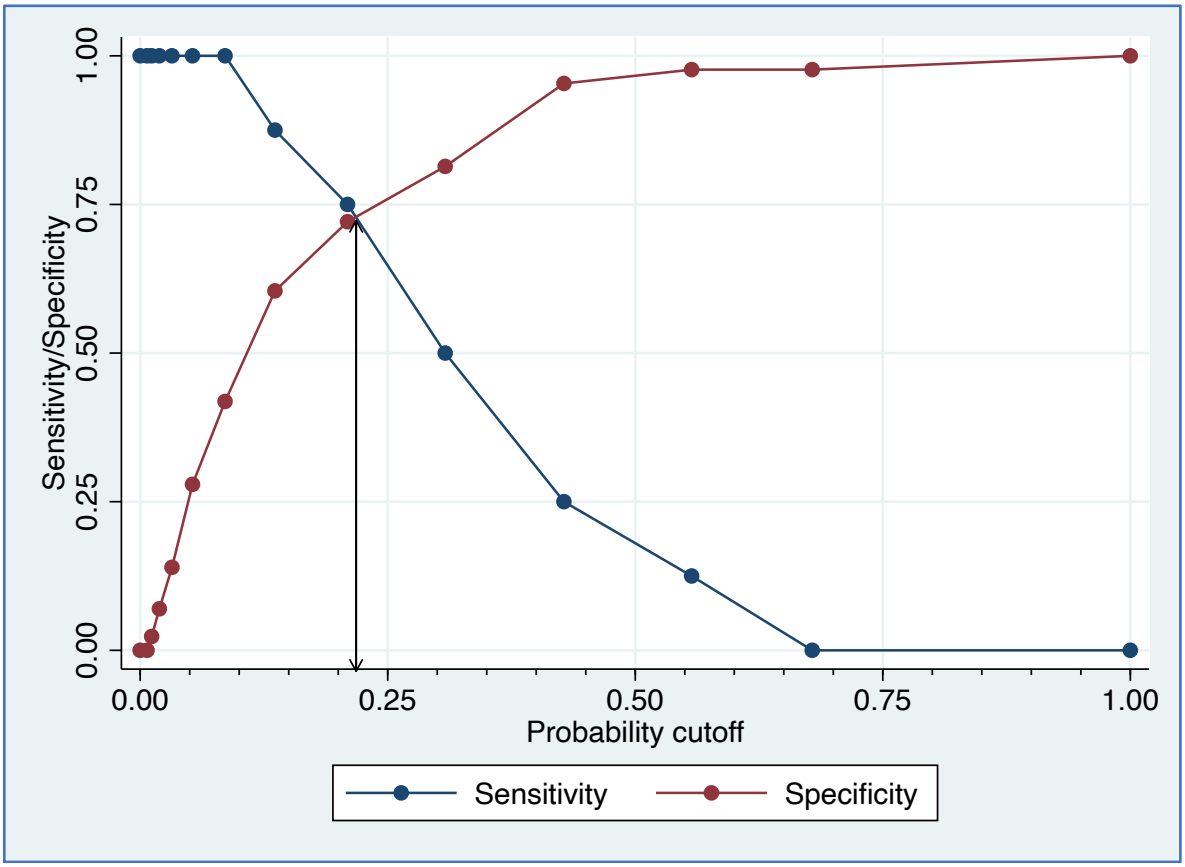

Figure 3. Intersection of PPV and NPV of LUS score to predict surfactant administration
LUS – lung ultrasound scan; NPV – negative predictive value; PPV – positive predictive value

APPENDICES

Appendix 1: Data Collection Instrument

Lung Ultrasound Case Record Form - ver2

Identifying data

Data base no…… Surname……

Infant Folder no…… DOB…… Time birth (24h) ……(hh:mm)

MATERNAL DETAILS

Age…….yr Gravidity….. Parity……. Multiple pregnancy Y / N

Illicit drug use: *Y / N* **Alcohol** (any) during pregnancy: *Y / N* **Smoker**: *Y / N*

Antenatal Care (Booked): *Y / N* **VDRL:** positive untreated / pos+fully treated / pos+partial treated/ negative

HIV: positive un-treated / positive on treatment / negative

Antenatal steroids: *Y / N If yes: Number Doses…….. Days between last dose and delivery: < 1 / 1-2 / 3 – 7 / > 7*

Hypertension (any) *Y / N* ***Antenatal or intrapartum MgSO4*** *Y / N* **Diabetes:** *Y / N*

Antenatal pyrexial illness/infection *Y / N* **Antenatal Antibiotics** *Y / N*

Other Maternal conditions *Y / N*

If Yes, 1. ……2……..…....3…….

LABOUR AND DELIVERY

Induced *Y / N* **Analgesia IV/IM within 4 hours of birth** *Y / N*

Mode delivery CS */ NVD / Vag Breech/ Instrumental*

Anaesthetic: Spinal/Epidural *Y / N* **General** Y /N

Spontaneous Prem (<37w) labour: *Y / N* **Prelabour ROM**: *Y / N* **PROM > 18h**: *Y / N*

Clinical Chorioamnionitis: *Y / N*

Intrapartum antibiotics: *None / Ampicillin / Erythromycin / Other……..*

Abnormal intrapartum event(s) *Y / N* **detail:……**

CLINICAL DETAILS AT BIRTH

Sex M / F / UK **Birth weight**…….gm **Weight category:** ELBW / VLBW / LBW **COH**:……..cm

Gestational Age……wks **Based on: Dates** Y / N **Early US ≤ 20 wks** Y / N **Ballard** Y / N **Foot length** Y / N

Apgar Score 1min: ….5min ……**Mask vent** *Y / N* **Intubated** Y / N **Chest Compressions** *Y / N* **Adrenaline** *Y / N*

Blood gas available *in 1st 60 min* ***Y / N*** If yes:

Result (worst):

cord / infant pH……(Kpa) pCO2……..(KPa) $BE_{(ecf)}$ …….. Lactate……mmol/l Hb…….g/dl

Temp at 1 hour measured Y / N **– if yes**: …… **℃**

Lung ultrasound scan procedure

Clinical respiratory diagnosis before LUS:

Respiratory distress syndrome (HMD) **Y / N** Pneumonia **Y / N** Transient Tachypnoea of Newborn (TTN) **Y / N**

Pneumothorax **Y / N** Other Pulmonary air leak *(pneumomediastinum/pneumopericardium)* **Y / N**

Time scan done……..(hh:mm). **Duration of scan**……

FiO_2 at scan:…….. Resp support at scan: **NCPAP / HFNC**

Resp distress at scan *(Resp Rate > 60/ Grunting/ Recessions (tracheal/subcoastal/intercostal)* **Y/N**

Data from Lung Ultrasound Report form completed by blinded reviewer

LUS SCORE

RIGHT		LEFT		
R1		L1		
R2		L2		
R3		L3		
Total R		Total L		Total R+L:

HMD Y/N (LUS score ≥ 6)

LUS Characteristics

Non-compact B-lines anywhere (any amount)	Y	N
B-pattern (≥ 3) anywhere	Y	N
Severe B-pattern (coalescent B-lines) anywhere	Y	N
Normal lung (A-lines only) anywhere	Y	N
Pleural lines abnormal: disappearance, irregularity, and coarse appearance	Y	N
Subpleural consolidations < 1cm	Y	N
Extended (beyond subpleural area) consolidations > 1cm	Y	N
Air bronchograms or consolidation beyond subpleural area anywhere	Y	N
Double lung point	Y	N
Lung point	Y	N
Absent lung sliding	Y	N
Absent lung sliding with B-lines present in same view	Y	N
Absent lung sliding and absent B-lines in same view	Y	N
If absent lung sliding – was there lung pulse in the same views	Y	N

TTN Y / N (One or more of the below = each scoring 1 point)
Double lung point (normal/B-pattern or B/severe B) **Y/N**
HMD score 1 - 6 (areas with normal lung / non compact B-pattern) **Y/N**
Gradient of echogenicity between inferior (zones 1vs 2 or 3) and superior areas with lower echogenicity in superior areas, including areas with non-compact B-lines and no area with extended consolidation **Y/N**

TTN score…….

Pneumonia *(diagnostic criteria)* **Y / N** (One or more of the below = each scoring 1 point)
Absent lung sliding **and** any **B-lines present** in same view **Y/N**
Absent lung sliding, absent B-lines but lung pulse present and no lung point in same view, **Y/N**
HMD score < 6 with pleural line abnormalities (disappearance / irregularity / coarse) or any lung consolidation, **Y/N**
Large (> 1cm) areas of lung consolidation with irregular margins without a B/severe B pattern **Y/N**

Pneumonia score……..

Pneumothorax Y / N
*Absent lung sliding and **B-lines absent** AND lung pulse **absent** or lung point **present –** in same view*
(If lung pulse present and lung point absent = no pneumothorax)

OUTCOMES

Respiratory interventions

Surfactant doses **0 / 1 / 2 / 3** Time 1st dose (hh:mm)……. FiO_2 1st dose…….Time 2nd dose**…….** FiO_2 2nd dose …….

Oxygen low-flow **Y / N** Oxygen high-flow **Y / N** NCPAP **Y / N** Intubated **Y / N** CXR **Y / N**

Conventional ventilation **Y / N** HFOV **Y / N** Chest Drain **Y / N** Needle aspiration **Y / N**

Steroids for CLD **Y / N**

Final Respiratory diagnoses and outcomes

Respiratory distress syndrome (HMD) **Y / N** Meconium aspiration **Y / N** Pneumonia **Y / N**

Transient Tachypnoea of Newborn (TTN) **Y / N** Pulmonary Haemorrhage **Y / N**

Pulmonary Hypertension **Y / N**

Pneumothorax **Y / N** Other Pulmonary air leak *(pneumomediastinum/pneumopericardium)* **Y / N**

Pulmonary interstitial emphysema **Y / N** Congenital diaphragmatic hernia **Y / N**

Congenital lung malformation **Y / N**

Duration intubated…….d Duration any resp support/O_2**…….**days. Highest FiO_2 first 24 h…….

Continued respiratory support: ≥ 28 days **Y / N** ≥ 36 weeks corrected gestation **Y / N** BPD **Y / N**

Cardiac interventions

Inotrope **Y / N** Steroids for hypotension **Y /N** Surgery for PDA **Y / N**

Medical treatment PDA **Y / N, if yes:** Diuretics **Y / N** Ibuprofen **Y / N** Paracetamol **Y / N**

Cardiac diagnoses and outcomes

HDSPDA confirmed on echo **Y / N**

Other cardiac diagnosis **Y / N** detail……

Infection interventions

Antibiotics **Y / N - If yes,** more than one episode **Y / N.** CSF sent **Y / N**

Treated at any time with: Ampicilllin **Y / N** Gentamycin **Y / N** Amikacin **Y / N** Meropenem **Y / N.**

Colistin **Y / N** Ceftazidine-Avibactam **Y / N** Penicillin G or Benzathine **Y / N** Anti-fungal **Y/ N** Other**……**

Infection diagnoses and outcomes

Congenital infection **Y / N If yes** HIV **Y / N** Syphilis **Y / N** CMV **Y / N** Rubella **Y / N**

Other **Y / N……**

Early Bacterial sepsis/meningitis (≤ 72h) **Y / N** Organisms ……

Late Bacterial sepsis/meningitis (>72h) **Y / N** Organisms ……

Fungal infection at any time **Y / N** Organisms **……..**

Highest CRP **…….** Congenital/perinatal TB infected **Y / N**

GIT interventions

laparotomy **Y / N** Abdominal drain/aspirate **Y / N** ileo/colostomy **Y / N**

GIT diagnoses and outcomes

Necrotising enterocolitis (Bells stage II or III) **Y / N** If yes, what grade: **IIa / IIb / IIIa / IIIb**

Spontaneous Focal Intestinal Perforation (not NEC) **Y / N** Short Bowel **Y / N** Other **Y / N**

Haematological diagnoses and interventions

Anaemia requiring blood transfusion **Y / N** Coagulopathy treated with plasma **Y / N** Thrombocytopaenia **Y / N**

Platelet transfusion **Y / N**

Neurological diagnoses and interventions

Seizures (aEEG-confirmed) **Y / N**

Periventricular-Intraventricular Haemorrhage **Y / N / no scan** worst grade **0 / 1/ 2 / 3 / 4**

Periventricular Leucomalacia **Y / N / no scan** worst grade **0 / 1 / 2 / 3 / 4**

Post Haemorrhagic Hydrocephalus **Y / N Other neurological diagnosis……..**

Metabolic diagnoses

Hypoglycaemia **Y / N** Hyponatraemia < 130mmol/ L **Y / N / UK** Metabolic Bone disease **Y / N**

Renal abnormalities Y / N – if yes: detail…….

Congenital malformation Y / N

If yes, list……

Nutrition and fluids

Mother's Breastmilk **Y / N** DEBM **Y / N** Formula milk **Y / N** IV fluids **Y / N** TPN **Y / N**

MORTALITY OUTCOME AT 2 MONTHS

Died before discharge / age two months (whichever comes first)

Y / N Age **Date and time**……Days …….. (decimal)

Cause of death:……

Appendix 2: Lung Ultrasound Report Form for Blinded Reviewer

Data base no……

LUS SCORE

RIGHT		LEFT		
R1		L1		
R2		L2		
R3		L3		
Total R		Total L		Total R+L:

HMD Y/N (LUS score ≥ 6)

LUS Characteristics

Non-compact B-lines anywhere (any amount)	Y	N
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Subpleural consolidations < 1cm	Y	N
Extended (beyond subpleural area) consolidations > 1cm	Y	N
Air bronchograms or consolidation beyond subpleural area anywhere	Y	N
Double lung point	Y	N
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Absent lung sliding	Y	N
Absent lung sliding with B-lines present in same view	Y	N
Absent lung sliding and absent B-lines in same view	Y	N
If absent lung sliding – was there lung pulse in the same views	Y	N

TTN Y / N (One or more of the below = each scoring 1 point)
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HMD score 1 - 6 (areas with normal lung / non compact B-pattern) **Y/N**
Gradient of echogenicity between inferior (zones 1vs 2 or 3) and superior areas with lower echogenicity in superior areas, including areas with non-compact B-lines and no area with extended consolidation **Y/N**

TTN score…….

Pneumonia *(diagnostic criteria)* **Y / N** (One or more of the below = each scoring 1 point)
Absent lung sliding **and** any **B-lines present** in same view **Y/N**
Absent lung sliding, absent B-lines but lung pulse present and no lung point in same view, **Y/N**
HMD score < 6 with pleural line abnormalities (disappearance / irregularity / coarse) or any lung consolidation, **Y/N**
Large (> 1cm) areas of lung consolidation with irregular margins without a B/severe B pattern **Y/N**

Pneumonia score……..

Pneumothorax Y / N
*Absent lung sliding and **B-lines absent** AND lung pulse **absent** or lung point **present –** in same view*
(If lung pulse present and lung point absent = no pneumothorax)

Appendix 3: Informed Consent Forms

INFORMATION AND INFORMED CONSENT FOR DATA COLLECTION

Lung ultrasound in preterm neonates with respiratory distress syndrome

To the mother/guardian of……(name)……(folder no)

I am a clinician/researcher seeking your permission to include your baby's data in a research study being done at Groote Schuur Hospital and University of Cape Town. The study is comparing findings of lung ultrasound (a special kind of imaging) in the first three hours of life with the outcomes and progress in preterm babies who require non-invasive support for their breathing.

The inclusion of your baby in this study will not involve any additional interventions. Since agreeing to be in the study only involves giving permission for your baby's data (results) to be collected, the medical management of your baby will be the same, whether or not you agree for your baby to be in the study.

It is your choice if you want your baby to be in this study. This form has information to help you decide whether or not you would like your baby to be included in the study.

You should not sign this document until you understand all of the information presented in the following pages and until all of your questions about the research have been answered to your satisfaction.

If you give consent for your baby to be in the study, your baby can leave the study at any time.

This study has been approved by both University of the Cape Town, Faculty of Health Sciences, Human Research Ethics Committee (HREC) and the Groote Schuur Hospital Management. This study will be conducted according to the universal ethical principles.

What is non-invasive breathing support and why do some preterm babies need it?

Non-invasive breathing support refers to provision of additional air and/or oxygen flow through short tubes into the nose – called nasal continuous positive airway pressure (nCPAP) or nasal cannula or high flow humidified nasal cannula (HFHNC). Preterm babies most often require support for their breathing because of delayed clearance of lung fluid after birth or because of insufficient secretion in the lungs of a substance called "surfactant" that helps the lungs expand. Breathing support may also be required if there is infection in the lungs, if the lungs have popped, if the lungs have an abnormal structure or with heart problems - these are less common.

What other treatments may preterm babies requiring non-invasive breathing support receive?

If oxygen requirements persistently increase above 30-40% in the first days of life, we expect that babies have insufficient surfactant and we may administer surfactant as a medication into the lungs using a tube. Babies may also be treated with antibiotics if they have other reasons to suspect possible infection. If babies do not improve after receiving surfactant, they may require the placement of a breathing tube into their lungs and support on a breathing machine – these babies will also require a chest xray to assess the lungs and position of the breathing tube.

What is lung ultrasound and is it standard?

Lung ultrasound is a procedure involving the placement of a small smooth rounded ultrasound probe against your baby's chest and taking pictures which appear on the screen of a connected computer. The probe is on the outside of the body, but it is able to take pictures of the inside of the chest, similar to a chest xray, but more easily and quickly, using a safer method than xray and providing different information. Lung ultrasound is increasingly routinely performed in neonatal units around the world. Lung ultrasound is included as part of the care of selected preterm babies in GSH neonatal unit who are less than 34 weeks gestation.

What is the purpose of this research study?

We have introduced lung ultrasound as part of the care of selected preterm babies in GSH neonatal unit who are less than 34 weeks' gestation and would like to measure the extent of its benefit when it has been performed during the first three hours of life. Your baby has already had a lung ultrasound.

We will determine how useful lung ultrasound is in determining the reason for breathing support and to determine if it can predict the need for surfactant.

The lung ultrasound findings are not being used to change the care of preterm babies in our unit – at this stage we are only collecting the data which will help us describe how useful lung ultrasound is and to decide if we should be using lung ultrasound to determine if and when we should administer surfactant.

What happens if I agree for my baby to be in the study?

1. We will collect information about your pregnancy, your baby's birth and your baby's clinical information and outcomes until age two months or discharge from hospital – whichever occurs first.
2. The data will be collected onto a paper form by doctors who are involved in your baby's care – the form will be kept in a locked cupboard
3. Data from the form will be entered into a password-protected computer and stored in a secure online database.
4. Data that identifies your baby will only be accessible to staff who are involved in the care of your baby.
5. The care of your baby will be identical whether or not you agree for your baby to be in the study.

Am I going to benefit from this research?

Participation in this study will not benefit you /your baby directly, however the results of the study may benefit babies in the future if lung ultrasound is shown to predict the need for treatment with surfactant more accurately and earlier than only oxygen requirement. More accurate and earlier diagnosis can reduce unnecessary treatment and improve benefit from earlier treatment by decreasing complications of delayed diagnosis. The data from this study may provide an opportunity to improve how we manage these babies in the future and possibly change the practice in hospitals around the Western Cape.

What are the risks and discomforts?

Lung ultrasound is a non-invasive, radiation free bedside and pain-free tool – we are performing it in the first three hours in babies who may benefit. Being in the study will not influence whether your baby receives ultrasound or not – your baby has already had a lung ultrasound. We are only seeking your consent to collect your baby's data.

Is there any compensation for participation?

You will not receive any payment or other compensation for participating in this study. There is also no cost to you for participation.

Confidentiality

All the information that we will collect from this study will be kept confidential. We are going to allocate and use a number instead of a name to record any information which may be accessible to researchers who do not usually care for your baby. Your baby will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

General questions

If you have any questions or concerns about the research, please feel free to contact the following main investigators:

Dr Fefekazi Mpisane-Jama or Professor Alan Horn
Groote Schuur hospital
Main Road, Observatory 7925
Tel: 021 404 6069

E-mail: MPSJEN001@myuct.ac.za or E-mail: alan.horn@uct.ac.za

Questions about ethics and rights as a research participant

If you require any information regarding your child's **rights as a research participant, or complaints regarding this research study**, you may contact Prof. M. Blockman, the Chairperson of the Faculty of Health Sciences Human Research Ethics Committee, which is an independent committee established to help protect the rights of research participants at (021) 406-6942.

CONSENT STATEMENT

Lung ultrasound in preterm neonates with respiratory distress syndrome

By Signing below, I agree that:

- I have read, or had explained the information contained on pages 1 – 3 of this document and I understand the information.
- I have had the chance to ask questions and they have been answered.
- I understand that taking part in this study is voluntary.
- I give permission to use and share my baby's health data as described in this document.
- I may choose for my baby not to be in the study or to leave the study at any time – if so, my baby will not be penalized or lose any benefits to which my baby is otherwise entitled.

…… Date……

Printed Name and Surname of the primary care giver (Mother /father/guardian)

…… Date……

Signature of the primary care giver (Mother /father/guardian)

…… Date……

Printed Name and Surname of the person taking consent

…… Date……

Signature of the person taking consent

My signature above confirms that I have fully explained the purpose and nature of this study to the above participant's Parent/Legal Guardian including the following:

- the aims, methods, institutional affiliations of the study and the study doctors;
- the anticipated benefits and potential risks of the study; and
- the Parent/Legal Guardian's right to abstain from their child's participation in the study or to withdraw consent for their child to participate at any time without reprisal.

A copy of this signed and dated information and consent form has been provided to the Parent/Legal Guardian.

Appendix 4: Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 June 2022

HREC REF: 335/2022

Prof A Horn
Division of Paediatric Neonatology
Room 63 H-46 OMB
Email: Alan.horn@uct.ac.za
Student: MPSJEN001@myuct.ac.za

Dear Prof Horn

PROJECT TITLE: DIAGNOSTIC UTILITY OF LUNG ULTRASOUND IN PRETERM NEONATES WITH RESPIRATORY DISTRESS AT A TERTIARY NEONATAL INTENSIVE UNIT IN THE WESTERN CAPE-
(MPHIL CANDIDATE-DR FEFEKAZI MPISANE-JAMA)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19. Please refer to guidance letter dated 02 February 2022 on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 June 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Fefekazi Mpisane-Jama will also be involved in this study.

Please quote the HREC REF 335/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

HREC/ref 335.2022

Appendix 5: Institution Approval Letter

Western Cape Government

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

Professor A. Horn
Division of Paediatric Neonatology

E-mail: alan.horn@uct.ac.za

Dear Professor Horn

RESEARCH PROJECT: Diagnostic Utility of Lung Ultrasound in Preterm Neonates with Respiratory Distress at a Tertiary Neonatal Intensive Unit in the Western Cape.

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 June 2023**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
n) Kindly submit a copy of the publication or report to this office on completion of the research.
o) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
p) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

Signed by candidate

pp
DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 10 August 2022
C.C. Mr. L. Naidoo, Mr. A. Mohamed, Dr. M. Ismail, Professor M. Harrison

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

Appendix 6: Author Guidelines for Journal

Contents

JOURNAL INFORMATION

For more information on individual Adis Rapid+ journals including aims and scope, publication fees, contact information, and Editorial and Advisory board members, please visit the journal websites.

Advances in Therapy
Cardiology and Therapy
Dermatology and Therapy
Diabetes Therapy
Infectious Diseases and
Therapy Neurology and
Therapy Oncology and Therapy
Ophthalmology and Therapy
Pain and Therapy
Pulmonary Therapy
Rheumatology and Therapy

Please note that there is a Rapid Service Fee associated with publication across the entire Adis Rapid+ journals portfolio. This is a **mandatory** fee that must be paid upon article acceptance. For more information on compulsory fees, please see each journal website, using the links above.
Information regarding fees can then be found under the *"Aims and Scopes"* heading on each of the journal websites.

PRESUBMISSION CHECKLIST

Manuscripts should be submitted through the Editorial Manager online submission system. Please ensure that your submission meets our editorial policies by following the below instructions. Prior to submission, please use the below checklists to make sure you have the necessary information and files that are required to submit your manuscript. We cannot proceed with the submission until we receive all of the necessary requirements outlined below.

Further information on how to submit your article can be found here.

Information Checklist

The below details should be given in the appropriate fields in the online submission system:

- ✓ Article type (see here);
- ✓ Article title;
- ✓ Author information, including affiliations, and email addresses for all authors;
- ✓ Abstract (including the trial registration number, if applicable);
- ✓ Three to ten keywords;
- ✓ Confirmation that your submission complies with the following requirements:
    - The manuscript is not being considered for publication by another journal, nor will it be submitted elsewhere while under consideration by this journal;

- The manuscript has not been published previously (partly or in full);
- No tables/figures/images/other material that infringe the copyright of another publisher/individual are included in the manuscript (or if there are such items included in the manuscript, permission to reproduce [both in print and online for the lifetime of product] has been sought and received for publication in this manuscript);
- All co-authors are aware of the submission to this journal, and agree to allow the corresponding author to serve as the primary correspondent with the editorial office and to review and sign off on the final proofs for publication;
- The authors whose names appear on the submission have contributed sufficiently to the manuscript (concept and planning of the work described; acquisition, analysis and interpretation of the data; drafting and/or critical revision of the manuscript; and approved the final submitted version of the manuscript) and, therefore, share collective responsibility and accountability for the manuscript;
- No deserving authors have been omitted from the authorship list;
- All persons who made substantial contributions to the manuscript but who do not fulfil the authorship criteria are listed with their specific contributions in the Acknowledgements section of the manuscript, and all persons named in the Acknowledgements section have given written permission to be named in the manuscript.

✓ Additional information (failure to provide this information at submission may lead to delays in processing):

- Name, email, postal address, telephone number, and VAT number (where applicable; for registered EU companies) for financial correspondence;
- Details of and reasons for any specific publication deadline;
- Information on where you heard about the journal;
- The email address of anyone, other than the corresponding author, who should receive manuscript correspondence throughout the publication process;
- Details of any digital features;
- Details of the ethics statements applicable to the study;
- If the trial was registered, please include details of the trial registration including a clinical trials number, beneath the abstract (e.g. *Trial registration: ClinicalTrials.gov identifier, NCT12345678).* For trials that were registered retrospectively, please also include the date of registration and the words “retrospectively registered” beneath the abstract. Trial registration is not mandatory; however, we strongly encourage prospective registration of clinical trials.
- *Advances in Therapy ONLY:* Whether you require the article to be published open access; all other journals in the portfolio are fully open access.

✓ Details (name, affiliation, and email address) of up to three suggested reviewers for your submission (optional). Recommended reviewers should not be from any of the authors' affiliations or institutions or have any potential conflicts of interests that may affect their ability to provide an unbiased review of the article. Please note that, although your help is appreciated and may speed up the selection of appropriate reviewers, the Editorial Team reserves the right to select reviewers.

File Checklist

The following files are needed during the submission process. Each item in the checklist should be saved as a separate file.

- ✓ Manuscript including title page, abstract, keywords, 4-5 key summary points, main text, acknowledgements, references, tables, figure legends, and line numbers;
- ✓ Figures (each figure should be submitted as a separate file either as a JPG or TIFF file);
- ✓ Any supplementary material (optional);
- ✓ Any digital features (optional).

PRESUBMISSION ENQUIRIES

Please contact the journal's Editorial Team to address any queries you may have prior to, during, or after manuscript submission. In particular, contact the Editorial Team regarding enquiries for manuscripts with specific, important publication deadlines, or in instances where you are unsure of a manuscript's suitability for the journal.

For enquiries specifically related to one of the Adis Rapid+ journals, you are also welcome to contact the Managing Editor directly (see links to journal-specific websites at the beginning of this document).

ARTICLE TYPES

The journals publish a variety of article types. All article types described below are subject to peer review.

Original Research/Brief Reports

We recommend that manuscripts reporting on original research conform to the CONSORT guidelines, whenever possible, although this is not mandatory. Research articles are welcome across the clinical research pathway (including post-marketing research, observational studies, and health economics and outcomes research).

As a guide, Original Research articles should be around, but not limited to, 4000 words.

Brief Reports describing a clinical study, or new insights into clinical management, diagnosis, or treatment are welcome. Brief Reports describe studies that are smaller in scale and patient numbers, and may report limited pilot data that warrant the need for further investigation.
Authors are encouraged to use these sections when submitting the manuscript: Introduction (including the research hypothesis), Methods, Results, Discussion, and Conclusion. As a guide, Brief Reports should be around, but not limited to, 2000-3000 words.

The abstract and main text of all Original Research articles and Brief Reports should be structured as follows: Introduction (including the research hypothesis), Methods, Results, Conclusion.

For all studies involving human participants, we encourage all authors to follow the Sex and

Gender Equity in Research (SAGER) guidelines, and to include sex and gender considerations where relevant. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully to prevent confusion between both terms. Article titles and/or abstracts should indicate what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the Discussion. We recommend that authors consult the full guidelines before submission.

Reviews

Comprehensive reviews of a specific drug, device, or particular area of interest are welcome. If conducting a review of the current literature, please provide details of the databases searched, the dates to which the search is limited, and search terms. Systematic reviews and meta-analyses should conform to the PRISMA guidelines, although this is not mandatory. The abstract and main text of systematic reviews and meta-analyses should be structured as follows: Introduction, Methods, Results, Discussion, Conclusion. If submitting a Review, please indicate in the title the format of the Review (e.g. systematic, narrative).). There is no word limit for Reviews submitted to the Adis Rapid+ journals.

Case Series

Manuscripts describing a number of interesting, unusual, or novel individual medical cases focusing on the same indication are welcome in the form of a Case Series. Manuscripts are encouraged to follow the CARE guidelines for reporting cases, although this is not mandatory. Authors should make clear the importance of their particular cases, summarise previous research in the condition, explain the implications for future therapy, and how the Case Series adds to the medical literature. Manuscripts must meet at least one of the following criteria to be eligible for consideration:

- Unreported or unusual side effects or adverse interactions involving medications;
- Unexpected or unusual presentations of a disease;
- New associations or variations in disease processes;
- Presentations, diagnoses, and/or management of new and emerging diseases;
- An unexpected association between diseases or symptoms;
- An unexpected event in the course of observing or treating a patient;
- Findings that shed new light on the possible pathogenesis of a disease or an adverse effect.

Case Series should have the following structure: Abstract; Introduction (including a summary of why the cases are unique/important with reference to relevant medical literature); Case presentations (including patient information, clinical findings, timeline, diagnostic assessment, therapeutic intervention, follow-up, and outcomes, etc.); Discussion; Conclusion(s) (including the primary “take-away” lessons from the case series); Acknowledgements; References. As a guide, case series should be around, but not limited to, 3000 words.

Consent to publish must be obtained from the patients or the patients' parents, relatives, guardian, etc. A consent form can be requested from the Editorial Team. Note: We do not require this form as part of the submission, but it must be declared in the manuscript that written informed consent for the publication of the patients' clinical details was obtained and that a copy
of the consent form is available for review by the Editor.

Case Reports

Please note that *Advances in Therapy* does not accept Case Reports.

All other Adis Rapid+ journals will consider unique individual Case Reports but these should meet the same eligibility criteria and ethical requirements regarding consent given above for Case Series. Manuscripts are encouraged to follow the CARE guidelines for reporting cases.

As a guide, Case Reports should be around, but not limited to 2000 words.

Commentaries

Commentary articles are designed to allow an author to put a particular topic/research into their own perspective, drawing on their own experiences and insights, and backing up their arguments with existing evidence. There is no mandatory structure and authors are encouraged to structure their Commentary in a way that best suits their voice. As a guide, Commentaries should be around, but not limited to, 2000-3000 words.

Patient/Physician Perspectives

These commentary-style articles are designed to highlight patient experiences and raise healthcare professional awareness of the patient perspective and best practices for patient-centricity. The first half of the piece is written by a patient, describing their experience of living with a particular condition. For example, day-to-day experiences, the journey to a correct diagnosis, response to treatment, psychosocial aspects of the condition, side effect management, quality of life issues, or anything that is important and relevant to them. This section may also be written (or co-written) by the carer or guardian of the patient. The second half of the article is written by an expert physician or any other healthcare practitioner(s). This would usually be the patient's own treating physician; however, if this is not possible, another healthcare practitioner who is familiar with the condition could write the accompanying perspective. This section may also be written (or co- written) by other healthcare professionals and should be underpinned with evidence referenced from available literature. As indicated above, these articles can include multiple perspectives and are not limited to patients/physicians. As a guide, Patient/Physician Perspectives should be around, but not limited to 2000-3000 words.

Physicians should discuss with their patients the potential consequences of identifiable personal and medical information being published open access, so that patients can choose in a fully informed way whether to co-author in an open access publication. If requested, patients/caregivers/parents can choose to remain anonymous.

An example of a Patient/Physician Perspective article can be found below: https://link.springer.com/article/10.1007/s40487-020-00132-2

Podcast Articles

Podcast articles follow a commentary style of publication, and typically feature a Q&A expert discussion with the author (or authors) around a topic of clinical interest, such as clinical data or real-life expert experience and opinions.

Adis Podcasts are published on SpringerLink. If open access, the podcast audio will also be published on Figshare and a number of popular podcast platforms (including Apple, Spotify, Deezer, and GooglePlay). Podcast articles are also indexed on PubMed.

The SpringerLink-hosted version consists of the audio podcast, along with the verbatim transcript. This transcript is typeset and published as a regular article within the journal with a DOI. Abstracts for Podcast articles are optional.

The journal strongly encourages authors to contact the relevant journal with a presubmission enquiry before initiating a Podcast article, and to read the Adis "*Guidelines for Digital Features and Plain Language Summaries*", which can be found under the submission guidelines on the relevant journal's homepage.

An example of a Podcast article is provided below:
https://link.springer.com/article/10.1007/s40120-021-00266-z

Trial Designs/Study Protocols

Study Protocols for any proposed or ongoing trials may also be submitted. All protocols will undergo peer review prior to publication. It is recommended that the article be structured as follows: Abstract (summarising the introduction [background/objectives], methods, planned outcomes); Introduction (background, objectives, trial design); Methods (study design, sample selection, measurements, planned outcomes, data collection, data analysis); Strengths and Limitations; Ethics; and Dissemination. For further information on protocol reporting, please read the SPIRIT statement. As a guide, Study Protocols should be around, but not limited to, 2000-3000 words.

Study Protocols are not only limited to clinical trials; they can also apply to real-world/observational studies or other types of future planned research.

Publication of original research relating to study protocols that have already been published in an Adis Rapid+ journal is entitled to a 20% discount on the journal's Rapid Service Fee. This should be highlighted in your cover letter when submitting.

Practical Approaches

Practical Approach articles intend to provide innovative and novel evidence-based practical guidance on difficult clinical management issues. Each article aims to provide a succinct and

accessible overview of a key topic for the broad range of healthcare professionals working with patients, including nurses and primary care physicians, and encompassing engaged patients and their caregivers where appropriate. The objective of these articles is to concisely review the most recent evidence relating to a clinical care situation and place this into a practical context. The use of flow charts, demonstrative videos, and visual material is encouraged in these articles to help readers digest the key information. As a guide, Practical Approach articles should be around, but not limited to, 2000 words.

Summary of Research Articles (SRAs)

A Summary of Research Article (SRA) is a standalone summary of a source article previously published in an Adis journal, or in a journal from another publisher. The SRA allows the key information to be understood more quickly and by a wider audience than that intended for the source article. It should provide a balanced and accurate representation of the study findings/source article: nothing key from the parent article should be left out and new content not previously included in the source article should not be added in.

All Adis journals can consider SRAs for publication. The SRA will usually be based on an original research source article; SRAs based on other source article types will be considered on a case-by- case basis.

We strongly encourage pre-submission enquiries for SRAs: please contact us with information regarding the source article, the proposed authors and target journal.

Intended readership: SRAs should be written for a readership that is less specialised than that intended for the source article. They are primarily intended for healthcare professionals (HCPs) who are non-specialists in the specific subject area of the source article, but they may also be of interest to other readers looking for a concise and accessible summary in plain language. Jargon, abbreviations, data-heavy tables and complex graphs should be avoided, while medical/scientific precision should be maintained.[1]

Authorship: SRAs submitted to the Adis journals for consideration must include at least one author from the source publication.[2] Other authors not previously involved in the primary publication are permitted but must meet ICMJE criteria for authorship.

Article details:

[1] Examples:
"Stomach" or "Abdomen" (not "tummy")
"Initial light sleep stage" (not "stage N1 sleep")

[2] Adis also publishes Adis-authored SRAs, selected and developed by the Editorial staff of Drugs & Therapy Perspectives: https://www.springer.com/journal/40267.
Please contact adisjournals@springernature.com copying Clare Cook (clare.cook@springernature.com) for further information.

- SRAs can either be graphic-based and formatted as a single figure with an introductory sentence linking to the figure, or text-based with figures/tables.
- The title of the article must include the term "Summary of Research:" as the prefix, followed by the title of the source article being summarised.
- There should be a brief abstract which includes a statement explaining that this is a summary of the source article.
- The first sentence in the main text should also state that this is a summary of the source article and include a citation to the source article. If this is a graphic-based summary, this sentence must conclude with "figure 1" (where figure 1 is the graphic summary).
- The source publication should be the primary (and usually only) reference.
- The SRA should not recycle segments of text from the source article. SRAs will be screened with plagiarism software in the same way as any other article type.
- SRAs should not include a Plain Language Summary abstract, as the SRA itself is a summary in plain language.
- Other article information requirements are as for a standard article in the journal, including Acknowledgements, Author information and Ethics declarations. Any funding or editorial assistance for the SRA should be declared. Further information on these requirements may be found in the relevant journal's Submission Guidelines.
- For a graphic-based SRA, the Adis logo and Peer Reviewed stamp should be included. This can be requested from the journal team prior to submission or can be added in during production.
- Colour combinations should enhance reader accessibility and not detract from the content.
- 'Commentary' should be selected as the article type at submission. This will be changed to 'Summary of Research' during production.
- The final complete article should be a maximum of 4 published pages in length.
- SRAs published open access are published under CC BY-NC copyright.

Permissions: We recommend that authors contact the publisher of the source article at the outset to seek permission to publish the SRA in an Adis journal. Authors wishing to include figures and tables that have previously been published are required to obtain the necessary permissions from the copyright owner(s), and to confirm that the necessary permissions have been granted when submitting the SRA. All material received without such evidence will be assumed to have been originated by the authors.

Post publication: All SRAs are published on SpringerLink and in a standard issue of the journal. In addition, SRAs are also included within a collection of all SRAs available on SpringerLink.

Guidelines

Guidelines provide a comprehensive guide to the optimum management of a disease, disorder, or situation which highlight clinically relevant considerations and recommendations. These articles may be affiliated with societies but this is not a requirement. If guidelines are from a particular society, this should be highlighted in the article title. For Guidelines, we also ask that the following disclaimer is included within the acknowledgements section of the article: "Springer Healthcare is not responsible for the validity of guidelines it publishes.". As a guide, Guidelines should be around, but not limited to, 10,000-15,000 words.

Letters to the Editor

Letters will be considered on a case-by-case basis and reviewed by the journal's Editorial Board. Letters should comment on a recently published article in the journal and are limited to one comment and one response by the authors of the original paper, should they wish to respond. As a guide, Letters to the Editor should be around, but not limited to, 1000 words.

TOPICAL COLLECTIONS AND SUPPLEMENTS

Adis Rapid+ journals welcome supplements. Material appropriate for supplements includes: sponsored meeting proceedings, roundtable discussions, workshop reports, case series, and collections of articles on the same topic.

The journals also support topical collections, which aim to collate articles on a certain topic, making them easily accessible to interested readers. Articles in a topical collection are published in a standard journal issue; however, they are also accessible through a dedicated topical collection page on the website.

Proposals for supplements and topical collections are welcome and should be addressed to journal specific Managing Editors (see list of journal specific links at the beginning of this document).

The peer review process for special/guest-edited issues and topical collections is the same as the peer review process of the journal in general. Additionally, if the guest editor(s) authors an article in their special issue/ collection, they will not handle the peer review process.

DIGITAL FEATURES

Adis journals can publish a range of peer reviewed digital features alongside articles, including animated abstracts, video abstracts (talking heads), slide decks, audio slides, instructional videos, infographics, podcasts/audio discussions, and animations. These features are designed to increase visibility, readership, and the educational value of the manuscript content. Digital features must provide an accurate representation of the article. For further information about digital features, please contact the journal editor (see "Contact the Journal" for email address), and see the "*Guidelines for Digital Features and Plain Language Summaries*" document via the journal website.

PREPRINTS

We encourage posting of preprints of primary research manuscripts on preprint servers, authors' or institutional websites, and open communications between researchers whether on community preprint servers or preprint commenting platforms. Posting of preprints is not considered prior publication and will not jeopardize consideration in our journals. Authors should disclose details of preprint posting during the submission process or at any other point during consideration in one of our journals. Once the manuscript is published, it is the author's responsibility to ensure that the

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FEES

For all Adis Rapid+ journals, authors are required to pay the mandatory Rapid Service Fee upon article acceptance. As *Advances in Therapy* is Open Choice, authors opting for open access publication in this journal will be required to pay an additional open access fee. The open access fee will be issued through a separate invoice. For full pricing information, please visit the journal websites.

MANUSCRIPT STRUCTURE

All articles should follow the guidelines below for the Title page, Abstract, Keywords, Key summary points, Introduction, Discussion, Conclusion, Acknowledgements, References, Figures, Tables, and Supplementary material. Original Research articles should also follow the guidelines for Methods and Results. Abstracts and Key summary points are not mandatory for Letters, Commentaries and Editorials and authors can use their discretion for the structure and headings used in these article types. Submissions are encouraged to conform to the standards outlined in the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals," prepared by the ICMJE.

General

Line Numbers: To facilitate the review process, we request that authors submit a line-numbered version of their manuscript.

Drug Names: When drugs are mentioned, the international (generic) name should be used. If the proprietary name is required, for example to distinguish between formulations, the manufacturer should be stated in full after the first mention of the proprietary name and the unregistered (™) or registered (®) trademark symbol should be used. The symbol does not need to be used subsequent to the first mention. The source of any new and experimental preparation should also be given.

Spelling, Abbreviations, Nomenclature, and Units: Authors may choose US or UK English spelling. However, this must be consistent throughout the manuscript. All standard and nonstandard abbreviations in the text must be defined at first mention and used consistently thereafter.
Symbols should not be used unless first explained in the text (reference guide: *Units, Symbols and Abbreviations*, Royal Society of Medicine, London). Highly sophisticated, specialist terms should either be defined or avoided. Intelligibility is a major aim of the journals. For substances, materials, and instruments, the correct designation and the manufacturer's name should be given. The city and country of the manufacturer should also be included. For units of measure (International System of Units) SI units should be used throughout, except where non-SI units are more common.

Title Page

The title page should include the following elements:

- *Title*: Should capture the essence of the manuscript in no more than 20 words (within reason). The title should be specific enough for electronic retrieval and searches. Where relevant, the title should include the drug name, indication, and study design. If appropriate, the country- or population-specific (e.g. pediatric) nature of the study should also be clear from the title. Where possible use generic drug names.

- *Author Details*: The name(s) of all authors and their institutional affiliation(s) and address(es). It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field, but in the absence of specific guidelines, authors are encouraged to follow the ICMJE authorship guidelines when considering authorship. All contributors who do not meet the selected criteria for authorship should be listed in the acknowledgements at the end of the manuscript.

- *Study Groups*: If a manuscript has been produced on behalf of a study group, this should be indicated by including the following text at the end of the author list: 'on behalf of [INSERT NAME] study group'. We then encourage the list of investigators to be included on the title page of the manuscript. This way the investigator's names will be included as collaborators on PubMed. If preferred, however, the list of investigators can be included in the Acknowledgments or Supplementary Material. When naming individual investigators or members of a study group (who are not authors on the paper), please ensure you have

permission from each individual to include their full name on the publication.

- *Correspondence Details*: At least one author should be designated as the corresponding author and is responsible for the submission of the article. Their email address and full correspondence address should be provided.

- *ORCID iDs:* Adis also encourages the use of ORCID iDs, which can be inputted when uploading a submission. To ensure that ORCID iDs are published in articles, authors should ensure that these are listed on the title page of the manuscript for each author (where required).

- *Prior Presentation:* Presentation at scientific meetings (in the form of abstracts or posters) does not constitute full publication. However, if any part of the manuscript has been previously shared, please highlight that this manuscript is based on work that has been previously presented. The statement should include details of where the contents was presented, (e.g. conference) including relevant dates and location.

Abstract

Each paper must include an abstract of up to 300 words that is understandable to the journal's readership without referring to the main text. Abstracts are mandatory for all article types except for Letters, Commentaries, and Editorials. For Original Research and Brief Reports, the abstract should be presented in a structured format (i.e. Introduction, Methods, Results, Conclusion).
Abstracts for Review articles do not need to be structured. Abstracts must reflect the content of the article accurately. The abstract should not cite any references. Readers should be able to understand why the study was done, the question asked, and how the study was carried out. The results must contain sufficient data for readers to evaluate the credibility of the conclusion. Not all of the data from the methods and results sections need to be presented. The conclusion should be an inference, not a summary. The trial registration number, if available, should be provided at the end of the abstract.

Plain Language Summaries (Optional)

Authors are welcome to submit a plain language summary (PLS) with their manuscript. A PLS is an effective tool to summarise your paper, extending the reach and impact that the paper can have, and making it accessible to a wider audience. The aim of the PLS is to assist in understanding the scientific content and overall implications of the manuscript. The summary should be aimed at non-specialists in the field, including members of the public and non-academics.

To be indexed on PubMed, the PLS should be no more than 250 words, and should be placed below the abstract.

- The summary should be based on the abstract of the paper and should be written in an easy-to-understand manner, using accessible language that does not patronise the reader;
- Sentences should be written in the active voice, rather than the passive voice, and should be short, clear sentences broken up into relevant sections;

- Keywords from the abstract should be used and defined where needed.
- Jargon should be avoided other than where absolutely necessary. In which case, it should be explained in full on first use;
- Abbreviations should be avoided.

Two examples are provided below:

- https://link.springer.com/article/10.1007%2Fs40271-020-00460-5
- https://link.springer.com/article/10.1007%2Fs12325-020-01377-z

Non-standard PLS, such as those longer than 250 words, graphical PLS, slide sets, or video PLS can also be accommodated. For more information on the different types of PLS, please read the "Author Information - Guidelines for Digital Features and Plain Language Summaries" document available to download on the journal website (under "Submission Guidelines").

Keywords

A list of 3–10 keywords must be given in alphabetical order after the abstract characterising the scope of the paper. These should include any drug names and indication(s) where appropriate.

Key Summary Points

Authors are required to provide 4–5 single-sentence bullet points, below the abstract, summarising their paper. Authors should use the following structure for Original Research articles:

Why carry out this study?

- Very brief background leading to the study, including for example disease population, economic burden, and/or unmet need. *(1–2 bullet points)*
- What did the study ask?/What was the hypothesis of the study? *(1 bullet point)*

What was learned from the study?

- What were the study outcomes/conclusions? (data) *(1 bullet point)*
- What has been learned from the study? This can be any outcome even if it contradicts the initial study hypothesis. If the findings were negative, neutral or purely confirmatory, how might this affect research and/or treatment in future? *(1–2 bullet points)*

For other article types (e.g. Reviews), 4–5 single-sentence bullet points summarizing the key messages from the paper should be provided. For Case Reports/Case Series, authors should state what is unique about the case and what it will add to the current literature. If you are unsure what should be included in the key summary points please contact the journal's Editorial Team for more information.

The key summary points will sit online alongside your article, and are intended to explain the value and relevance of your research. The summary points will undergo peer review with your article and so must purely reflect the content within the article.

It is **mandatory** to provide key summary points for all articles types except for Letters, Commentaries, and Editorials. Not providing them will delay your submission being sent for peer review.

Introduction

The introduction should provide a brief review of pertinent literature and cite relevant findings that led to the current study. Be careful not to exclude relevant findings by other investigators. It should discuss the unknowns that remain to be determined or controversies that exist in the literature. Controversial findings should be presented in the introduction if they are important to the rationale for the study. Explain why the study was undertaken; if appropriate, state the proposed hypothesis. End the introduction with a stated aim or question, preferably expressed as a testable hypothesis. For example, if the study is aimed at identifying the color of apples, or asks
what color are apples, state “We hypothesized that apples will be green rather than red.” The reason for this hypothesis should be contained in the rationale.

Methods

The methods should provide sufficient detail such that another investigator can repeat your research. This section should describe the procedures used and provide sufficient information (subjects, measurements, statistical analyses) so that a reader can evaluate the credibility of results and interpretation in the light of possible methodological limitations. If authors have used similar methodologies that have been used in a previous study, this should be acknowledged and appropriately referenced. Findings should be quantified when possible, and presented with appropriate indicators of measurement error or uncertainty (e.g. confidence intervals). Any statistical software used during analysis should be identified. If any scales or questionnaires have been used, authors should check that the appropriate permissions to use such resources have been acquired and this permission should be clearly stated at an appropriate place in the manuscript.
For literature reviews, authors should include the details of how their search was conducted, i.e. when the search was conducted; inclusion/exclusion dates; search terms; databases searched. Authors should also include details of how many papers/abstracts were retrieved, and how many were discarded and why. Authors should always consider clarity for other researchers when detailing how and why a study was done in a particular way.

> **All articles must contain a statement of ethics compliance within the main body of the text**, for example, within the methods (or any other appropriate section for articles without a specific methods section). This should be the same as the statement given in the *“Compliance with Ethics Guidelines”* sub-section in the acknowledgements (see below).

Results

The results should present the findings in a logical progression through the research process. Tell a story; this does not necessarily mean that findings will be presented in the chronological order in which they were discovered. Results concerning the primary testable hypothesis should be
presented first, followed by any secondary outcomes. Do not save the “best” for last. Provide a sufficient interpretation of data to lead the reader from one concept to the next, but leave the

detailed analysis for the discussion section. The results must contain a sufficient summary of data.

Data should be presented as concisely as possible, if appropriate, in the form of tables and/or graphs. Avoid duplication of information particularly of data within text, figures, tables, or in figure legends. Save the comparison of the findings with other studies for the discussion.

Discussion

The discussion should include a summary of the main findings from most to least important, including a statement on whether the results are consistent with the stated hypothesis. Avoid a simple reiteration of background information and results. Discuss how the results confirm or contrast with published literature. If the results differ, discuss the possible reasons for this. Details of methodology and results of published literature may be appropriate here. Avoid reviewing literature outside the scope of the study. Discuss the significance and implications of the new data. Having developed the rationale to define the limits of current knowledge, how does this new information advance understanding? The inferences made throughout the discussion must be written bearing in mind the constraints of the methodological limitations of the work. Any issues of bias should be mentioned, and how these have been dealt with in the design and interpretation of the study. A paragraph detailing the limitations of the study must be included in the discussion section.

Conclusion

The conclusion is an inference. Within the constraints of the limitations of the study, the authors may speculate regarding the significance of the findings, recommendations, and future research. However, authors should not make any conclusions that are not supported by the results.

Acknowledgements

Information relating to all Editorial policies can be viewed here.

All manuscripts must contain an acknowledgements section, given before the reference list, which contains the following information, where applicable.

Funding

Please list all sources of funding received for the study and publication of the article. All institutional and corporate funding sources should be mentioned. The names of funding organizations should be written in full, including the city and country. If no funding was received this should also be declared.

E.g. “Sponsorship for this study and Rapid Service Fee were funded by Pharma Ltd.” or “No funding or sponsorship was received for this study or publication of this article.”

Please ensure that clinical trials sponsored by pharmaceutical companies follow the guidelines on Good Publication Practice (GPP).

Medical Writing, Editorial, and Other Assistance

The acknowledgements should include the specific contributions of all persons who have

substantially contributed to the work reported (e.g. technical assistance, data collection, analysis, writing, or editing assistance) but who do not fulfill the selected authorship criteria. Ideally, authors should obtain permission from all persons listed in the acknowledgements, although this is not mandatory. Medical writers are considered as legitimate contributors and their names, roles, affiliations, and source of funding must all be detailed in the acknowledgements. An example of suitable text for acknowledging the contribution of a medical writer to a manuscript would be:

"Editorial assistance in the preparation of this article was provided by Dr. Jane Doe of Medical Communications Inc. Support for this assistance was funded by Pharma Ltd."

Authorship

The publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In the absence of specific guidelines, it is recommended to adhere to the following guidelines for authorship*:

All authors whose names appear on the submission should have:

1) Made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;
2) Drafted the work or revised it critically for important intellectual content;
3) Approved the version to be published; and
4) Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved.

*Based on/adapted from:
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