Perinatal Management of Extreme Preterm Birth at the Threshold of Viability

A Framework for Practice

The Clinical Programme in Neonatology
The Neonatal Clinical Advisory Group
The Faculty of Paediatrics
The Institute of Obstetricians and Gynaecologists
The National Women and Infants Health Programme

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Executive Summary

- This consensus document has been developed in consultation with a multi-disciplinary group of experts in light of improving outcomes for infants born at the threshold of viability and changes in clinical practice; and supersedes the 2006 document.
- This document refers to infants born between 23+0 and 24+6 weeks' gestation.
- It recommends a change in the threshold of fetal viability from 24+0 weeks to 23+0 weeks gestation.
- Initiation of life sustaining treatment is not recommended for infants born less than 23+0 weeks' gestation.
- Decisions relating to the provision of care to infants and mothers at this gestation 23+0 – 24+6 weeks should take into consideration all confounding clinical factors. It should reflect the desires of the parents and should hold the outcome of both the mother and the infant at its core.
- Women that are deemed to be at risk of delivering an extremely preterm infant should be transferred to a tertiary centre with a neonatal intensive care unit (NICU) on site to avoid out-born delivery. Transfer should occur without delay to allow adequate time for antenatal counselling and for the provision of the highest standard of perinatal care to the mother and infant(s).
- Decision making relating to the care of women and infants born at this gestation should not be based on gestational age alone but should take into account all confounding factors that may affect viability.
- For infants for whom life sustaining treatment is not planned palliative care should be provided in accordance with the *HSE National Standards for Bereavement Care following Pregnancy Loss and Perinatal Death.*
- It is appropriate to explain to parents that resuscitation efforts may not be successful and active care may be redirected to palliative care if the infant's clinical condition is unresponsive to efforts or is deteriorating.

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Introduction

The threshold of fetal viability has progressively lowered over time. In the 1970s, the limit was set at 28+0 weeks' gestation. In the 1980s, the survival of infants less than 28+0 weeks' gestation started to exceed 50%. Over the subsequent 30 years it decreased to 24+0 weeks' gestation. More recently, a further reduction in the threshold of viability to 23+0 weeks' gestation has been proposed by many perinatal centres and working party groups.[1, 2, 3].

In 2006, the Faculty of Paediatrics, Royal College of Physicians of Ireland (RCPI) stated that *'it is acceptable not to resuscitate newborns with a birth weight less than 500g and/or under 24 weeks' gestation.*[4] This consensus statement is now being reviewed in light of recent advances in neonatal intensive care. The two key issues that dominate the debate on fetal viability are; the survival rate and the risk of long term neuro-disability. If there is a strict cut-off for 'viability' a proportion of infants who did not have life sustaining measures initiated after birth would have survived without moderate to severe disability. On the other hand, if there is a more proactive approach there will be increased numbers of survivors with disability.[5]

This document has taken into account the opinions of neonatologists, obstetricians, neonatal nurses, midwives and parents. The psychological and emotional toll of a very preterm birth on the parents and extended family is a major consideration. The shock, uncertainty, and the intimidating nature of the neonatal intensive care unit (NICU) can be very stressful for families. All members of the perinatal team should be fully cognisant of the impact that the process will have on the infant's family.

Aim

This document relates to the perinatal care of infants born in Ireland between 23+0 and 24+6 weeks' gestation. It does not relate to decision making around termination of pregnancy.

The purpose of this position paper is to bring a greater level of clarity and consistency to the perinatal and neonatal management of extremely preterm infants.

Background

Prematurity is a major cause of neonatal mortality and morbidity. The incidence of preterm birth is 7%. Two thirds of preterm births occur spontaneously and the remaining third take place electively for either maternal or fetal indications.

There is general agreement that most perinatal centers in first world countries would initiate life sustaining measures and subsequent intensive care for infants born at

24+0 weeks' gestation and beyond. At the other end of the spectrum it is generally agreed that resuscitation should not be administered to infants at 22 weeks' gestation, although the 2019 UK, BAPM Framework for Practice paper proposes considering resuscitation for infants born from 22+0 weeks' gestation.[6]

The grey area is at 23+0 and 23+6 weeks' gestation. Overall the number of infants born in Ireland at this gestation is small, but the acuity level is high. The Vermont Oxford Network (VON)/Neonatal Intensive Care Outcomes Research and Evaluation (NICORE) Irish data for the 5-year period from 2014 to 2018 reports that there were 120 infants born at 23 weeks and 191 infants born at 24 weeks' gestation.[7] The survival, in Ireland at 23 weeks is increasing; 19% (2014), 30% (2015), 37% (2016), 47% (2017) and 33% (2018). The corresponding rates for infants born at 24 weeks' gestation are 50% (2014), 65% (2015), 56% (2016), 56% (2017) and 51% (2018). For consistency, the literature refers to completed weeks' gestation and the next 6 days e.g. 24 weeks refers to 24 weeks and 0 days through to 24 weeks and 6 days.[8]

Gestational Age	2014 No. of survivors/ No. of liveborn infants (%)	2015 No. of survivors/ No. of liveborn infants (%)	2016 No. of survivors/ No. of liveborn infants (%)	2017 No. of survivors/ No. of liveborn infants (%)	2018 No. of survivors/No. of liveborn infants (%)
<22 weeks	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/6 (0%)	0/5(0%)
22 weeks	0/18 (0%)	0/16 (0%)	0/19 (0%)	0/16 (0%)	0/12(0%)
23 weeks	4/21 (19%)	9/30 (30%)	10/27 (37%)	7/15 (47%)	9/27(33%)
24 weeks	18/36 (50%)	22/34 (65%)	25/45 (56%)	21/37 (56%)	20/39(51%)
25 weeks	25/35 (71%)	33/43 (77%)	39/50 (78%)	27/50 (54%)	32/41(78%)
26 weeks	28/43 (65%)	30/37 (81%)	34/39 (87%)	31/39 (79%)	50/54(93%)
27 weeks	54/57 (95%)	40/46 (87%)	47/49 (96%)	60/69 (87%)	46/52(88%)
28 weeks	75/83 (90%)	82/90 (91%)	77/83 (93%)	83/88 (94%)	65/69(94%)
29 weeks	89/95 (94%)	94/99 (95%)	80/85 (94%)	74/83 (89%)	70/75(93%)
30 weeks	68/71 (96%)	65/65 (100%)	62/66 (94%)	84/87 (97%)	51/53(96%)
31 weeks	44/49 (90%)	64/68 (94%)	49/50 (98%)	52/54 (96%)	31/34(91%)
32 weeks	36/39 (92%)	35/37 (95%)	34/36 (94%)	28/31 (90%)	36/39(92%)
>32 weeks	46/48 (96%)	51/55 (93%)	39/42 (93%)	34/37 (92%)	25/30(83%)
Total	**487/597 (82%)**	**525/622 (84%)**	**496/593 (84%)**	**501/612 (82%)**	**435/530(82%)**

Table 1. Gestational age breakdown and survival to discharge of ROI infants reported to VON[7]

Factors other than gestational age will affect outcome, such as birth weight, exposure to antenatal steroids, gender, multiplicity of pregnancy, poor in-utero growth, and presence of congenital anomalies; and whether delivery occurs in a specialist centre. At 23 weeks' gestation, every additional day in the womb increases survival by 3%.[9] The estimated weight of the fetus is relevant.[7] At 23 weeks' gestation the 50th centile weight is 565g (girls) and 604g (boys). At 24 weeks' gestation the 50th centile weight is 659g (girls) and 706g (boys). Girls have a week advantage over boys in terms of maturity.[10] Multiple births do less well than singleton births. In some jurisdictions, the presence of other confounding factors is used along with gestational age to stratify infants into extremely high and lower risk category groups when deciding whether to initiate life sustaining treatment after birth.[6]

Outcomes at the threshold of viability

Survival to discharge and in particular survival without severe disability, is seriously compromised by extreme prematurity. Mortality and serious morbidities are multifactorial in extremely preterm infants, however increasing gestational age has a protective effect. Survival < 22 weeks' gestation has not been documented in the Republic of Ireland (ROI), nor have published outcomes from the NICORE group reported any survivors delivered before 23+0 weeks' gestation.[7]

Analysis of data from the VON database from all 19 tertiary, regional and peripheral units in Ireland, published in 2017, provides local Irish outcome data for infants at the extremes of viability. However, it was acknowledged that the small numbers of deliveries per annum could lead to significant variation from year to year, and so it was recommended that three to five years of data should be collected before a more meaningful analysis of the national dataset be undertaken. This three year report was published in 2018 and found that infants born at 22-23 weeks' gestation in the ROI had a 23% higher mortality risk than their VON counterparts (Standarsised Mortality Ratio (SMR) =1.23, 95% CI: 1.02-1.44); and this higher rate of mortality was due to a higher proportion of infants who were not administered resuscitation. Infants born at 24-27 weeks' gestation in a tertiary centre in the ROI did not experience higher than expected mortality (SMR=1.10, 95% CI: 0.8-1.23) but those born in non-tertiary units had a 70% higher mortality risk (SMR=1.70, 95% CI: 1.25-2.15).[7]

Many health services have adopted a PAGE approach to estimating survival in very premature infants. PAGE refers to **P**rognosis for **A**verage **G**estation age **E**quivalent, and provides survival data by completed week of gestation.[11] NICORE outcomes by gestational age for Irish infants delivered are summarised below (Table 2). Infants born between 24+0 and 27+6 weeks in ROI do not have a higher SMR compared to VON (SMR=1.14, 95% CI: 0.95-1.34) (but there is a difference in those born in tertiary

versus non-tertiary centers). Our numbers are small but infants Babies < 24 weeks' have a significantly higher SMR compared to VON.[7]

Gestational Age	2014 No. of survivors/ No. of liveborn infants (%)	2015 No. of survivors/ No. of liveborn infants (%)	2016 No. of survivors/ No. of liveborn infants (%)	2017 No. of survivors/ No. of liveborn infants (%)	2018 No. of survivors/No. of liveborn infants (%)
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26 weeks	28/43 (65%)	30/37 (81%)	34/39 (87%)	31/39 (79%)	50/54(93%)

Table 2. NICORE outcomes by gestational age for Irish infants delivered

Developmental impairment and disability are recognised adverse outcomes for survivors of extreme prematurity. Severe disability is generally defined as one or more of the following: severe cognitive impairment with an IQ below 55, severe cerebral palsy, blindness or severe hearing impairment. Although collation of national formal neurodevelopmental outcome data is in progress, this is not yet available. Composite outcome data from major studies of neurodevelopmental outcome at the thresholds of viability suggest that 1 in 4 survivors delivered before 24+0 weeks, 1 in 7 between 24+0 and 25+6 weeks and 1 in 10 survivors born after 26+0 weeks will have severe disability. The rates of infant survival with either no, or mild disability at 6 years are much lower (30% of survivors at 23 weeks, 40% of survivors at 24 weeks and 45% of survivors at 25 weeks' gestation).[12]

Risk assessment, Decision making and Ethical considerations

Where possible, decision making around whether or not to initiate life sustaining treatment to an extremely preterm infant should be made with ample time prior to delivery. All confounding factors that may affect viability, as well as gestational age (as listed previously) should be considered and discussed between the obstetric and neonatal teams, and the infant's parents before a decision is made. For caregivers the principles of ethics and good clinical practice should be central to care provision at this time. [13-23] At the core of any decision to provide or withhold active care is the question; if life sustaining measures are initiated is the most likely prognosis acceptable for the baby, the parent(s) and the caregivers.[20, 21]

Several factors including chance of survival, quality of life, pain and suffering and the wishes of the parents and family unit all need to be considered. It is essential that the

parent's' views as to the best interests of the infant are considered centrally in any decisions made.[13,23] However, caregivers are not always obliged to provide interventions to an infant that are not in their best interest or to withhold interventions that are beneficial.[22,24, 25]

The UK (BAPM) [6] and Australian (Queensland) [11] guidelines differ slightly in their approach to assessing which infants to institute life sustaining treatment after birth. The latest draft for consultation of the UK, BAPM guidelines proposes *a risk-based approach* to decision making where gestational age (including infants from 22+0 to 26+6 weeks') and other factors that may affect infant and maternal health are considered equally when counselling parents. In this document infants' risk is stratified into three groups; extremely high risk, moderate to high risk and lower risk. For infants in the extreme or moderate risk group the likelihood of surviving without severe impairment is less than not and the decision to initiate life sustaining treatment is guided by the wishes of the family. Active treatment is recommended for infants in the lower risk group.

The Queensland guidelines (2014) makes recommendations for infants born at each week of gestation from < 23 weeks' up to > 25 weeks' gestation. The authors place more emphasis on risk assessment for gestational age using the PAGE framework while considering all relevant prognostic factors to support their decision making and counselling. Broadly, active treatment is optional for infants born at 23-24 weeks gestation and should be guided by parental preference and life sustaining treatment is usually recommended for infants from 25+0 weeks. They do not recommend active treatment for infants born < 23+0 weeks' gestation. [11]

To our knowledge, in Ireland there have been no reported survivors of infants born < 23+0 weeks' gestation. The survival rate for infants born at 23 and 24 weeks gestation is improving but the number of infants are small and survival figures lag behind international figures.[7]

<u>Recommendations:</u>

- We do not recommend initiating life sustaining treatment to infants born at < 23+0 weeks' gestation.
- In general, life sustaining treatment is recommended for most infants born at ≥ 25+0 weeks' gestation unless there are comorbid factors that make intact survival unlikely.

When deciding whether to initiate life-sustaining treatment to an infant born between 23+0 weeks and 24+6 weeks' gestation it is essential to:

- Review all available clinical information and best local and international evidence to prognosticate as best as possible for the infant and mother.
- Consider all confounding factors that may influence viability in the decision making.
- Individualize perinatal care in the best interests of each mother and infant.

Communication and documentation

All communication with parent(s) should be open, honest and consistent with the information given to other parents in similar clinical situations. If there is sufficient time counselling and decision making should occur in the antenatal period, and should be delivered by caregivers who are experienced in caring for extremely preterm infants. Parents should be allowed time to consider their options following discussion with the perinatal teams. All discussions and decisions should take into consideration the parent(s) hopes and expectations in the context of their social and cultural background, and their understanding. If required, an interpreter should be provided to communicate clearly with a family. Management plans should be communicated to all relevant caregivers and documented clearly in the maternal healthcare records. Care plans should be reviewed and updated by the clinical teams in consultation with the family as time evolves and/or if the clinical situation changes.

Obstetric management of preterm labour and birth

The diagnosis of preterm labour

The diagnosis of preterm labour is both difficult and uncertain in the presence of a closed cervix and intact membranes. Mild, irregular contractions are a normal finding at all stages of pregnancy. There is no threshold contraction frequency that reliably identifies women who will progress to established labour.

Only 5-10% of women who present with preterm contractions will continue to actual labour and delivery.

A mother is considered to be in established preterm labour when she has progressive cervical dilatation with regular contractions.

The newer techniques of ultrasound measurement of the cervical length[26] and vaginal fetal fibronectin (fFN) are increasingly being used in the prediction of preterm labour. They are particularly helpful when in-utero transfer to a tertiary perinatal centre is being considered.

Fetal Fibronectin (fFN): When the fFN test is positive it is a predictor of preterm labour.[27] The fFN is secreted by fetal cells. It is found at the interface of the fetal sac and the uterine lining. It is believed that the protein keeps the sac glued to the uterus. When considering intrauterine transfer, a threshold value 200 ng/ml. can be used. The test is contraindicated if there is vaginal bleeding or ruptured membranes as these

clinical situations cause false positive results. The test can be repeated weekly in women at high risk of preterm labour.

Partosure (placental alpha macroglobulin 1): An alternative biomarker to fFN. It has a similar negative predictive value but a slightly better positive predictive value.[28]

QUiPP app (quantitative innovation in predicting preterm birth): The QUiPP app incorporates a number of factors and measurements and calculates the risk of preterm birth within the next 7 days. The factors include previous preterm birth, fetal fibronectin, and cervical length measurements. Using a 5% risk of preterm delivery within 7 days, up to 90% of unnecessary admissions can be avoided.[29]

Antenatal steroids

Preterm infants born following administration of antenatal corticosteroids have an increased chance of intact survival, improved fetal lung maturation, a decreased risk of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, sepsis, cerebral palsy, severe disability and retinopathy of prematurity.[30-35]

The evidence for the use of antenatal steroids is robust. At 23 weeks' gestation, death or impairment is reduced from 90.5% to 83.4%, at 24 weeks from 80.3% to 68.4%, and 25 weeks from 67.9% to 52.7%.

Dexamethasone/Betamethasone 12mgs intramuscular, two doses, 12 hours apart if time allows.

<u>Recommendations</u>:

Following multi-disciplinary team input, consideration of all factors affecting prognosis and discussions with the parent(s) (as detailed previously):

- If preterm delivery is likely and there is a plan to commence life sustaining interventions at birth antenatal steroids should be administered from 23+0 weeks' gestation.
- Caregivers may consider administering steroids at 22+5 weeks' gestation in anticipation of life sustaining interventions from 23+0 weeks' with the understanding that active treatment will not be initiated before 23+0 weeks'.

Magnesium sulphate

Administration of Magnesium sulphate should be considered in women in established preterm labour (cervical dilatation > 4cms with regular contractions).

It is associated with a reduced risk of cerebral palsy (RR 0.69; CI 0.54-0.87 NNT 63), substantial gross motor dysfunction (RR 0.61; CI 0.44-0.85) and reduced risk of composite outcome of death and cerebral palsy in the infants (RR 0.85; 95%CI 0.74-0.98).[36]

Recommendations:

- Magnesium sulphate is recommended for women between 23 and 32+0 weeks' gestation who are in established preterm labour or those having a planned preterm labour within 24 hours.
- The initial dose is a 4g intravenous bolus followed an intravenous infusion of 1g per hour until birth or for 24 hours.

Maternal antibiotic administration

Antibiotics are commonly administered to mothers in suspected preterm labour. The decision is guided by the clinical condition of the mother and the fetus. Suspected or confirmed clinical chorioamnionitis with a maternal temperature of ≥ 38 C, foul smelling liquor, leucocytes or bacteria in the amniotic fluid, is an indication for antibiotics.

When suspected preterm labour is associated with intact membranes and no sign of infection, intrapartum GBS antibiotic prophylaxis should be considered.[37]

Tocolysis

Tocolytics are medications used to suppress labour. Their use has been debated for many years without firm conclusions. The Royal College of Gynaecology (RCOG) states that it reasonable not to use tocolytics as there is no clear evidence that they improve outcome. However, they can be considered while waiting for the completion of the course of antenatal steroids or for intrauterine transfer.

Atosiban (Tractocile) is the most commonly used agent. It is an Oxytocin antagonist. The patient is administered an initial bolus followed by an infusion of up to a maximum of 48 hours.[38 39]

Fetal monitoring

At present there is no evidence that continuous or intermittent fetal heart rate monitoring is of benefit for infants at the threshold of viability. Physiological control of fetal heart rate and the resultant features seen on the CTG trace differs in the preterm fetus versus a term fetus making interpretation difficult. Fetal heart rate decelerations in the absence of uterine contractions often occur in the normal preterm fetus between 20 and 30 weeks gestation.

Fetal scalp electrodes are not routinely used under 34 week's gestation. Similarly, fetal blood sampling should not be performed prior to 34 weeks gestation.

Intrapartum monitoring would be deemed appropriate during the labour if active intervention with emergency caesarean section and neonatal intensive care is being contemplated. Monitoring should be used with caution and interpretation left to senior experienced obstetricians.

Mode of delivery:

Caesarean section is commonly considered less traumatic for preterm infants but the evidence is not robust.[40-42] Routine caesarean section is not recommended for a periviable gestation birth alone as it has not been shown to improve survival. There is limited retrospective data providing some support for caesarean section for malpresentation.

Two-thirds of very preterm births are spontaneous and one-third are elective. Caesarean section is more likely in the latter because the birth is being precipitated by an underlying maternal or fetal condition.

In general, caesarean section does not improve neonatal survival or reduce intraventricular haemorrhage. If the presentation is cephalic and there are no additional risk factors, the aim is a vaginal delivery.

The risks to the mother's short and long-term health need to be considered. This is particularly the case when the neonatal outcome for the very preterm infant is guarded.

Preterm labour is frequently associated with malpresentation. At gestations under 28 weeks the lower uterine segment is not well formed. A transverse incision of the upper segment may be necessary. This is associated with increased blood loss, increased post-operative morbidity and increased risk of scar dehiscence in a future pregnancy.

The mode of delivery should be individualised. It should take into account the well-being of the mother and the fetus, and the likelihood of neonatal survival.

Delayed cord clamping:

Delayed cord clamping is recommended for preterm births < 32 weeks' gestation. The usual interval between infant birth and period of delayed cord clamping is 60 seconds whereas immediate cord clamping is 5 seconds. In term infants, 80 mls of blood is transferred from the placenta to the infant in the first minute with only a small additional amount after that time. The amount transferred to a preterm infant would be proportionately less.

Clamping the cord after the infant has taken first breaths allows the placental circulation to maintain venous return and ventricular preload, enabling a smoother transition [43].

In the Australian placental transfusion RCT delayed clamping resulted in a 2.7% increase in haematocrit.

Also, there was a non-significant reduction in mortality.[44]

Place of delivery and in-utero transfer

Premature infants born at hospitals without NICU facilities who are transferred after birth ("out-born") die more frequently and have less favourable outcomes than

infants who are born at hospitals with NICU facilities ("inborn") [11,45,46].Neonatal survival of extremely preterm infants is improved if they are born at hospitals with the appropriate level of neonatal intensive care. Women likely to deliver a premature infant for whom life sustaining interventions are planned, or might be initiated, should therefore be transferred to a tertiary centre with a NICU without delay ("in-utero transfer" of a potentially premature infant).

Preventing out-born delivery of preterm infants should be a priority for both the referring and admitting hospitals. The aim of transfer is to optimise the conditions around birth. It does not mean that infants will inevitably be resuscitated at birth, admitted to the NICU or that efforts will be made to achieve survival of the infant at any cost. Careful assessment of the mother should be undertaken by a senior member(s) of the obstetric team at the referring hospital prior to transfer to ensure that transfer is safe; and that she is unlikely to deliver in transit. Prompt assessment of women in threatened preterm labour is critical. Delays in assessment in a time-critical situation may cause a potential window for transfer to be missed.

<u>Recommendations</u>

- If preterm birth is likely and if stabilisation and life-sustaining interventions are planned or may be a possibility, prompt in-utero transfer is recommended.
- If life-sustaining interventions are to be initiated at a specific gestation – e.g. 23^{+0} weeks' gestation, transfer should occur prior to this gestational age to ensure arrival at or before the specified gestation.
- A clear explanation of the reason for transfer should be communicated to the family and they should be informed that transfer to a tertiary neonatal will not guarantee active resuscitation.
- The case must be discussed with the appropriate teams at the referring and accepting hospitals and maternal and neonatal bed availability must be confirmed **prior to transfer.**

Neonatal Management

Delivery room management

For infants born between 23+0 and 25+0 weeks' gestation for which life sustaining treatment is planned stabilisation in the delivery room should be regarded as an emergency. A neonatal team should attend including healthcare professionals with the required level of experience in neonatal resuscitation. This team should preferably be led by a Consultant Neonatologist/Paediatrician, senior registrar or Advanced Nurse Practitioner (ANP). If may also be appropriate for an experienced clinician(s) to attend the birth of an extremely preterm infant for whom life sustaining support is not planned to provide support to the parents and staff after birth and to oversee the palliative care plan. Where gestational age is uncertain, or the parent(s) are undecided/unclear about their desire to initiate resuscitation it may be appropriate to initiate life sustaining interventions until the clinical course or parent preference becomes clearer.

Resuscitation

- If resuscitation is intended, refer to the ILCOR guideline and Neonatal Resuscitation Programme. [46, 47]
- Provide palliative care from birth to those infants for whom resuscitation interventions are not initiated, or are unsuccessful – refer to HSE palliative care document.[48]
- If parental wishes are unclear or unknown at the time of birth consider the circumstances particular to the case and it may be appropriate to initiate life sustaining measures until more information has been established.

References

1. Royal Australasian College of Physicians. Decision-making at the end of life in infants, children and adolescents. 2008. www.racp.edu.au
2. Wilkinson AR, Ahluwalia J, Cole A, Crawford D, Fyle J, Gordon A et al. Management of babies born extremely preterm at less than 26 weeks' gestation: A framework for clinical practice at the time of birth. Arch Dis Child Fetal Neonatal Ed. 2009;94:F2-5
3. ACOG Practice Bulletin: Clinical management guidelines for obstetricians-gynaecologists: Number 38 Sept 2002. Perinatal care at the threshold of viability. Obstet Gynecol 2002;100:617-24
4. Neonatal Subcommittee of the Irish Faculty of Paediatrics. Statement on Perinatal Care at the Threshold of Viability 2006
5. Sheldon T. Dutch doctors change policy on treating preterm babies. BMJ 2001;322:1383
6. Perinatal management of extreme preterm birth before 27 weeks of gestation: A Framework for Practice. Oct 2019. British Association of Perinatal Medicine. In conjunction with the Royal Colleges of Obstetricians and Gynaecologists and Paediatrics and Child Health, the British Maternal and Fetal Medicine Society, the Royal College of Nursing, the Royal College of Midwifery, MBRRACE-UK, Bliss and Sands.
7. Corcoran P, Drummond L, Twomey A, Murphy BP, Greene RA, on behalf of NICORE Republic of Ireland. Mortality risk amongst very low birth weight infants born in the Republic of Ireland, 2014-2016. Cork: National Perinatal Epidemiology Centre 2018. Copyright © National Perinatal Epidemiology Centre, 2018.
8. Raju TN, Mercer BM, Burchfield DJ, Joseph GF. Periviable birth: Shriver summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health & Human Development. J Perinatol 2014;34:333-42
9. Skupski DW, Greenough A, Donn SM, Arabin B, Bancalari E, Vladareanu R. Delivery mode for the extremely premature fetus: a statement of the prematurity working group of the World Association of Perinatal Medicine. J of Perinatal Medicine 2009;37:583-586
10. ACOG Practice Bulletin: Clinical management guidelines for Obstetrician-Gynecologists: Number 38, Sept 2002. Perinatal care at the threshold of viability. Obstet Gynecol 2002;100:617-24
11. Queensland Clinical Guideline: Perinatal care at the threshold of viability. Queensland Clinical Guidelines Steering Committee. Statewide Maternity and Neonatal Clinical Network. September 2014
12. Marlow N, Wolke D, Bracewell MA and Samara M for the EPICure Study Group (2005) Neurologic and developmental disability at six years of age after extremely preterm birth *N Engl J Med* 352: 9–19

13. Beauchamp TL CJ. Principles of Biomedical Ethics. Fifth ed: Oxford University Press; 2001.
14. Paris JJ, Graham N, Schreiber MD, Goodwin M. Has the emphasis on autonomy gone too far? Insights from Dostoevsky on parental decisionmaking in the NICU. Camb Q Healthc Ethics. 2006;15(2):147-51.
15. Doyle LW. Evaluation of neonatal intensive care for extremely-low-birth-weight infants. Semin Fetal Neonatal Med. 2006;11(2):139-45.
16. Doyle LW. Neonatal intensive care at borderline viability--is it worth it? Early Hum Dev. 2004;80(2):103-13.
17. Buchh B, Graham N, Harris B, Sims S, Corpuz M, Lantos J, et al. Neonatology has always been a bargain--even when we weren't very good at it! Acta Paediatr. 2007;96(5):659-63.
18. Meadow W, Reimshisel T, Lantos J. Birth weight-specific mortality for extremely low birth weight infants vanishes by four days of life: epidemiology and ethics in the neonatal intensive care unit. Pediatrics. 1996;97(5):636-43.
19. Meadow WL, Lantos J. Epidemiology and ethics in the neonatal intensive care unit. Qual Manag Health Care. 1999;7(4):21-31.
20. Kopelman LM, Kopelman AE. Using a new analysis of the best interests standard to address cultural disputes: whose data, which values? Theor Med Bioeth. 2007;28(5):373-91.
21. Kopelman LM. The best interests standard for incompetent or incapacitated persons of all ages. J Law Med Ethics. 2007;35(1):187-96.
22. Bioethics A. Guidelines on forgoing life sustaining medical treatment. Pediatrics. 1994;93:532-6.
23. Bell EF. Noninitiation or withdrawal of intensive care for high-risk newborns. Pediatrics. 2007;119(2):401-3.
24. Institute for Patient and Family centred care. What is patient and family centred health care. 2010. http://www.ipfcc.org
25. Warrick C, Perera L, Murdoch E, Nicholl RM. Guidance for withdrawal and withholding intensive care as part of neonatal end of life care. Br Med Bull. 2011; 98:99-113.
26. O'Hara S, Zelesco M, Sun Z. Cervical length for predicting preterm birth and a comparison of ultrasonic techniques. Australas J Ultrasound Med 2013;16:124-34.
27. Lockwood CJ, Senyei AE, Dische MR et al. Fetal Fibronectin in cervical and vaginal secretionsas a predictor of preterm delivery. N Engl J Med 1991;325;669-74
28. Kennedy C, O'Dwyer V. Predicting spontaneous preterm birth. Ir Med J 2019;112:964

29. Watson HA, Carter J, Seed PT, Tribe RM, Sennan AH. The QUiPP App. A safe alternative to a treat-all strategy for threatened preterm labour. Ultrasound Obstet Gynecol 2017;50:342-346.
30. Royal College of Obstetricians and Gynaecologists. Antenatal corticosteroids to reduce neonatal morbidity and mortality. Green-top Guideline No. 7. 2010.
31. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004454. DOI: 10.1002/14651858.CD004454.pub2.
32. Waldemar A, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz R, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA. 2011; 306(21):2348-2358.
33. Park CK, Isayama T, McDonald SD. Antenatal Corticosteroid therapy before 24 weeks of gestation. Obstetrics and Gynecology 2016; 127(4):715-725
34. Yim CK, Tam M, Chan HL, Tang SM, Sunny CL, Yin WK. Association of antenatal steroid and risk of retinopathy of prematurity: a systematic review and meta-analysis. British journal of Ophthalmology 2018; 102(10):1336-1341
35. Sotiriadis A, Tsiami A, Papatheodoru AA. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. Obstetrics and Gynecology 2015;125(6):1385-1396
36. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Systematic Reviews 2009, Issue 1. Art. No.: CD004661. DOI:10.1002/14651858.CD004661.pub3.
37. Hughes RG, Brockelhurst P, Steer P et al. Prevention of early-onset GBS infection. RCOG Green Top Guideline 2017 No 36.
38. Prevention of preterm birth, preterm labour and delivery guideline. Royal Cornwall Hospitals NHS Trust. July 2020
39. Klumper J, Breebaart W, Roos C, McAuliffe F et al. Study protocol for a randomised controlled trial for Atosiban versus placebo in threatened preterm birth: the APOSTEL 8 study. BMJ Open 2019:029101
40. Perinatal Management of Pregnant Women at the threshold of Infant Viability. RCOG Scientific Impact Paper No. 41 (2014).
41. Periviable birth obstetric care consensus. AJOG 2017;130:e187-198
42. Preterm labour and birth. NICE 2015.
43. O'Donnell C. The timing of cord clamping for preterm infants. N Engl J Med 2017;377:2488
44. Tarnow-Mordi W, Morris J, Kirby A et al. Delayed versus immediate cord clamping in preterm infants. N Engl J Med 2017;377:2445-2455

45. Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: The EPICure 2 study. Arch Dis Child Fetal Neonatal Ed 2014; 99:F181-F188.
46. Wyllie J, Perlam JM, Kattwinkel J,Part 7: Neonatal Resuscitation:2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation
47. American Heart Association. *NRP: textbook of neonatal resuscitation.* American Academy of Pediatrics, 7th edition, 2016.
48. National Standards for bereavement care following pregnancy loss and perinatal death. Health Service Executive, Ireland. August 2016

Appendix 1. Preterm Neurodevelopmental outcome at 2 years corrected age. The National Maternity Hospital, Dublin; 1997 – 2016. *(courtesy of Marie Slevin, Developmental Psychologist at NMH)*

Gestational Age	Severe Delay/Disability	Mild Delay	Normal	Advanced	**Total**
23 wks	3 (30%)	2 (20%)	5 (50%)	0%	**10**
24 wks	10 (20%)	8 (16%)	24 (48%)	7 (14%)	**49**
25 wks	13 (16%)	15 (18%)	41 (50%)	13 (16%)	**82**
26 wks	18 (15%)	17 (14%)	61 (51%)	23 (19%)	**119**
Total	**44 (17%)**	**42 (16%)**	**131 (50%)**	**43 (17%)**	**260**

Appendix 2. Ethical Principles

Classical ethical teaching highlights four key principles[14]; autonomy, beneficence, non-maleficence and justice. Other key element to be considered is the best interests' standard.

Autonomy

It is accepted that parents hold their child's interests' paramount and therefore have the right to act on behalf of their child. This parental autonomy is better described as parental authority. The objective information approach or expertise model involves providing parents with facts and empowering them to make an informed decision about intervention or non-intervention. Caregivers essentially avoid making any recommendation. The doctor's role is seen as more facilitative than directive and this approach places ultimate emphasis on parental autonomy.

The opposite of the parental authority approach is the 'broad shoulders/paternalistic approach'. It has been argued that the burden of having to make this decision is too much for parents and that decision making in the context of critical illness is different from decision making at other times. Proponents of this approach claim most peoples' thought processes are distorted when faced with critical illness. Some argue that for parents "these decisions are tormented situations, situations fraught with anguish, ambiguity and doubt" and asserts that "they are, at best, an awful and unwelcome burden". They advocate that we might "acknowledge parental reluctance to make such a decision and accept parents desire to avoid being forced to". Neither this "broad shoulder" overly paternalistic approach nor the parental authority approach is the most appropriate way to address these complex issues and a shared decision making model is proposed.

Beneficence

Beneficence is as 'an action done to benefit others; the principle of beneficence refers to a moral obligation to act for the benefit of others'.[15] The concept implies taking positive steps to help others, and not merely refraining from harmful acts (non maleficence). The physician assumes a role specific obligation of beneficent treatment to his patient. The prognostic uncertainty that is present when one first encounters a preterm infant at the limit of viability is often what makes decision making at these times so difficult. Clearly the survival of a child without any long-term problems is of great benefit to the child, parents, family unit, and healthcare professionals caring for the child and society at large. However, the survival of a child with significant neurodevelopmental disability brings its own challenges. This raises the important concept of the 'best interest's standard' and will be discussed later.

Non maleficence

The principle of non-maleficence is an obligation not to inflict harm on others.[14] This principle raises important issues in the care of the extreme preterm infant, such as withdrawing versus withholding treatment, ordinary versus extraordinary means, and the doctrine of double effect. The rule of double effect makes a very important distinction between intended and merely foreseen events. There are four conditions which must be met for an act with a double effect to be justified.

1. The nature of the act. The act in itself must be good
2. The intention. The agent intends only the good effect. The bad effect is foreseen, tolerated, and permitted, but it must not be intended
3. The distinction between means and effects. The bad effect must not be a means to the good effect
4. Proportionality between the good effect and the bad effects. The good effect must outweigh the bad effect.

Distributive Justice

The term distributive justice refers to; fair, equitable, and appropriate distribution determined by justified norms.[14] Neonatal intensive care for extremely-low-birth-weight (ELBW, 500-999 g) infants must be continuously evaluated to determine that it is effective, efficient, and available to those who need it. Two quantifiable outcomes are commonly used to analyse the cost effectiveness of NICUs: the total years of life saved (cost/year) and "quality adjusted" years of life saved.[16] Some studies have suggested that NICU care may not be cost effective for the tiniest babies due to the high costs per survivor.[17] More recent evaluations have shown that NICUs have become more cost effective as they become more clinically effective i.e. there are now more survivors at each weight specific category including the most immature babies.[18] One way of addressing the efficacy of NICU is to look at the number of bed days per survivor. Meadows[19, 20] compared bed days in survivors versus non survivors. They found that most of the bed days and hence most of the money spent was on survivors. Even for the tiniest babies more than 80% of the bed days were spent on survivors. Most neonatal survivors will be productive citizens: costs per quality adjusted life year saved being about 1/100 of the cost of acute adult coronary care.[16, 17] There should be no discrimination based on age, sex, race or social class.

Bests Interests Standard

In adult medicine decisions are made on the basis of an autonomous decision or in the case of a previously competent but now incompetent adult in the form of an advance directive or substituted judgement. For those who have never been competent a decision is made by a proxy, and in the case of the newborn this is generally the parent (or on occasion the state). The standard that is often applied is the best interest standard.

Kopelman[21] has described three aspects of the best interest standard - best interests as a threshold, best interest as an ideal and best interest as demonstrating reasonableness. The first is an operational threshold. This sets negative limits below which we may not go. The second is recognising our duty to promote the good of children. The third is doing what is reasonable considering the conditions, taking account of our abilities, authority and limits. When interpreting the Best Interests Standard three necessary features need to be analysed;[22]

1. Decision makers should use the best available evidence to assess the person's immediate and long-term interests and set as their prima facie duty the option that maximises overall benefits and minimises harm
2. Decision makers must meet a minimum standard i.e. at least good enough is determined by what a reasonable and informed person of good will regard to be acceptable were they in the persons' circumstances
3. Decision makers should make choices compatible with duties to the incompetent patient.

This standard has both subjective (values, views and perceptions of the decision makers) and objective (sound logical medical and scientific views and arguments) features. The principle is used by many professional organisations. The AAP Committee on Bioethics[23] acknowledges the parents' right to refuse treatment but also recognises that right is limited by the interests of the child: "Medical professionals should seek to override family wishes only when those views clearly conflict with the interests of the child". A consensus statement from AAP Fetus and Newborn[24] on the non-initiation or withdrawal of intensive care highlighted the following key elements: (1) direct and open communication between the health care team and the parents of the child with regard to the medical status, prognosis, and treatment options; (2) inclusion of the parents as active participants in the decision process; (3) continuation of comfort care even when intensive care is not being provided; and (4) treatment decisions that are guided primarily by the best interest of the child.

Best interests are generally assessed by determining the competing interests i.e. comparing the benefits and burdens of a proposed course of action and arriving at the best option. It is the prognostic uncertainty at the limit of viability that makes decision making in this context extremely difficult. It is important that frank and open communication take place between the parents and physicians when assessing the child's interests.