

## Performance and Safety of STAR Glycaemic Control in Neonatal Intensive Care: Further Clinical Results Including Pilot Results from a New Protocol Implementation

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Abstract: Elevated blood glucose concentrations (BG) (Hyperglycaemia) are a common complication of prematurity in extremely low birth weight neonates in the neonatal intensive care unit (NICU), and are associated with increased mortality and morbidity. Insulin therapy allows glucose tolerance and weight gain to be increased. However, insulin therapy is commonly associated with a significant increase in low BG events (hypoglycaemia), which is also associated with adverse outcomes. Controlling BG levels via nutrition restriction reduces infant growth and is thus undesirable. STAR (Stochastic TARgeted) is a model-based glycaemic framework that mitigates the risks of hypoglycaemia through quantification of current insulin sensitivity and future variability. From August 2008 to December 2012 40 patients totaling 61 glycaemic episodes were treated with STAR in the NICU (STAR-NICU). Percentage time in the clinically targeted 4.0-8.0 mmol/L band was 62%, a 14% increase compared to retrospective data and hyperglycaemia (BG>10.0mmol/L) was halved. Overall incidence of severe hypoglycemia (BG<2.6 mmol/L) was slightly increased from 0.4% to 0.7%, and a concomitant increase in the number of patients experiencing severe hypoglycaemia (8 of 62 control episodes in comparison to 1 of 25 retrospective). Results from 5 patient episodes under the new STAR-GRYPHON protocol were significantly better, with 83% of measurements in the targeted band (35% better than retrospective data and 17% better than original STAR NICU protocols), and 0% incidence of BG<4.0 mmol/L. STAR-GRYPHON is expected to maintain this level of tight glycaemic control. Thus, model based control can be safely and effectively used to control BG in extremely premature infants in intensive care.

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### 1. INTRODUCTION

Hyperglycaemia (elevated blood glucose (BG) levels) is a common complication of prematurity in neonatal intensive care units (NICUs) (Beardsall et al., 2010). In the NICU, hyperglycaemia has been associated with greater mortality (Hays et al., 2006, Hall et al., 2004, Kao et al., 2006) and morbidity, such as increased risk of infection (Bistrrian, 2001, Kao et al., 2006), intraventricular haemorrhage (Hays et al., 2006), length of hospital stay (Hays et al., 2006, Hall et al., 2004, Alaedeen et al., 2006), retinopathy of prematurity (Blanco et al., 2006), and ventilator dependence (Alaedeen et al., 2006).

There is no clinical best practice treatment method for hyperglycaemia, or accepted threshold (Alsweiler et al., 2007). BG is often controlled by varying nutritional input, but a reduction in nutritional input may restrict infant growth (Thabet et al., 2003, Alsweiler et al., 2012), and is associated with adverse neurodevelopmental outcomes (Ehrenkranz et al., 2006). Insulin therapy to treat hyperglycaemia allows greater glucose intake and weight gain in neonates (Bauer et al., 1991, Ostertag et al., 1986, Binder et al., 1989), but often results in increased incidence of low BG levels, hypoglycaemia, (Alsweiler et al., 2012, Beardsall et al.,

2008), which have been associated with adverse neurodevelopment outcomes (Lucas et al., 1988). Fixed or ad hoc protocols are often utilised, which lack patient specificity and thus fail to consistently manage the variability in patient response to insulin over time and between patients (Le Compte et al., 2013, Chase et al., 2011).

STAR (Stochastic TARgeted) is a model-based glycaemic control framework which has shown promising results in both adult and NICU care applications (Fisk et al., 2012, Le Compte et al., 2012). STAR uses a physiological model-based estimate of whole body insulin sensitivity (SI) to describe a patient's current metabolic state, and potential future variability. Predictions of likely changes in insulin sensitivity allow possible BG outcomes to be determined for a particular treatment. Thus, treatments can be selected based on a quantitative targeting of a desired outcome and risk of moderate hyperglycaemia.

STAR is used as a standard of care in Christchurch Women's Hospital NICU, New Zealand. This paper compares retrospective insulin therapy data with prospective STAR patients and the first patients under a revised version of STAR.

## 2.0 METHODS

### 2.1 Clinical procedures

Premature neonates received insulin therapy under the STAR protocol as a standard of care in Christchurch Women's Hospital, New Zealand. STAR has been implemented in a computer based application, and more recently through the use of beside tablet computers with a specialised touch-screen data entry interface.

The clinical implementation cycle is shown in Figure 1. Up to date insulin and nutrition rates and BG measurements are entered into the computer interface, which uses this data to calculate current SI and select a treatment based on SI forecasts. This treatment is given, and at the end of the measurement interval the next BG measurement is entered into the tablet, alongside any changes in nutrition or insulin, and another treatment is calculated.

Infants are started on STAR when they become hyperglycaemic (2 BG > 10.0 mmol/L within 4-6 hours). Blood samples are taken from a central umbilical line, if available, or from heel pricks every 2-4 hours. BG is determined using a Bayer 850 blood gas analyser (Bayer AG, Leverkusen, Germany). Insulin is always delivered as an infusion through the same line as the main dextrose fluids. Insulin concentration is calculated based on infant weight, such that 0.05 U/kg/hr = 0.20 mL/hr, and infusions are given in steps of 0.01 U/kg/hr.

Nutrition rates are clinically determined, and are not normally adjusted for glycaemic control. Typically, neonates receive the bulk of their nutrition via total parenteral nutrition (TPN) with 10% dextrose. Medications, such as dobutamine and morphine, are commonly infused with 5% dextrose. Enteral boluses of expressed breast milk (EBM) are used as soon as it is available, starting at 0.5mL every four hours, with increasing volume and frequency as tolerated. All nutrition sources and rate changes are considered by the model-based algorithm, and nutrition regimes over the next measurement interval are considered when calculating a treatment.

A neonate is taken off STAR when BG is in the target range (4-8 mmol/L), no insulin has been given in the last 6 hours, and the infant is determined to be glycaemically stable. An infant may be restarted if hyperglycaemia recurs.

### 2.2 Model dynamics

The NICING (Neonatal Intensive Care Insulin-Nutrition-Glucose) model (Le Compte et al., 2010a, Lin et al., 2011) describes glucose-insulin dynamics in the extremely preterm neonate. The rate of change of blood glucose ( $G$ ), in [mmol/L/min], is defined in Equation 1:

$$\dot{G} = -p_c G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_c Q(t)} + \frac{P_{ex}(t) + EGP * m_{body} - CNS * m_{brain}}{V_{g,frac}(t) * m_{body}} \quad (1)$$

Insulin-mediated glucose clearance is determined by insulin sensitivity ( $SI$ ), units [L/mU/min] and non-insulin-mediated

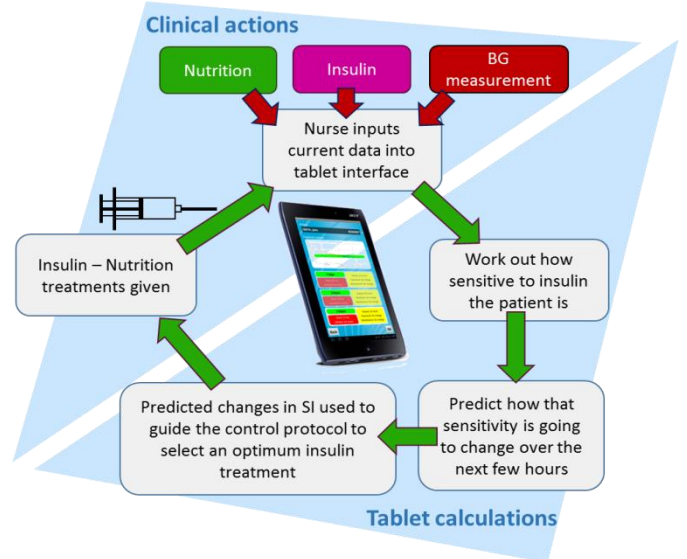


Figure 1: Clinical implementation of STAR glycaemic control

uptake including kidney clearance ( $p_G = 0.0030$  [min<sup>-1</sup>]), and a central nervous system (CNS) uptake ( $CNS = 0.088$  mmol/kg/min). Glucose inputs include exogenous glucose ( $P_{ex}(t)$  [mmol]) and endogenous production ( $EGP = 0.284$  mmol/kg/min).  $m_{body}$  is the body mass, and  $m_{brain}$  the brain mass (approximated as 14% of  $m_{body}$ ).  $V_G$  is the volume of distribution of glucose, and  $\alpha_G$  saturates glucose uptake. This is zero for neonates (Farrag et al., 1997).

The rate of change of plasma ( $I$ ) and interstitial ( $Q$ ) insulin (units [mU/L/min]) are defined in Equations 2-4:

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + (1 - x_L) u_{en} \quad (2)$$

$$u_{en} = I_B e^{-\frac{k_I u_{ex}}{V_I}} \quad (3)$$

$$\dot{Q} = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_C Q(t)} \quad (4)$$

Plasma insulin is cleared via the liver ( $n_L = 1.0$ /min, saturated by  $\alpha_I$ ), the kidney ( $n_K = 0.150$ /min) and transport into interstitial fluid ( $n_I = 0.003$ /min). Insulin enters the system exogenously ( $u_{ex}$  [mU/min]) or endogenously ( $u_{en}$  [mU/min]) via pancreatic secretion in Equation 3 (basal secretion  $I_B = 15$  mU/L/min, interstitial transport rate  $k_I = 0.1$  min<sup>-1</sup>, first pass hepatic extraction  $x_L = 0.6$ ). Insulin leaves interstitial fluid through degradation ( $n_C = 0.003$ /min).  $V_I = 0.047$ L is the volume of distribution of insulin.

Appearance of glucose via the enteral route is modelled by two intermediate compartments, the stomach ( $P_1$  [mmol]) and the gut ( $P_2$  [mmol]), and is described:

$$\dot{P}_1 = -d_1 P_1 + P(t) \quad (5)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{max}) + d_1 P_1 \quad (6)$$

$$P_{ex}(t) = \min(d_2 P_2, P_{max}) + PN(t) \quad (7)$$

Where P is enteral glucose delivery to the stomach, and PN is parenteral glucose delivery. Transport rates between the stomach and gut, and gut and blood ( $d_1 = 0.0347/\text{min}$  and  $d_2 = 0.0069/\text{min}$  respectively) are limited to a maximum flux ( $P_{max} = 6.11 \text{ mmol}/\text{min}$ ).

SI is patient-specific and time-varying, describing a patient's current metabolic state. It is fit on a retrospective hour-to-hour basis, and in addition to being a marker of peripheral insulin sensitivity, SI also incorporates uncertainty around patient-specific endogenous insulin and glucose production.

SI is forecast using stochastic forecasting based on population data, as shown in Figure 2. Kernel density models are used to generate distributions of likely SI outcomes at any given current SI (Le Compte et al., 2010b). BG outcome distributions are generated from SI distributions for a given insulin and nutrition treatment.

### 2.3 Protocol definition

To determine a baseline insulin sensitivity (SI) the infant is started on 0.05 U/kg/hr insulin for 2 hours. From then on, current SI is used with stochastic forecasting models based to determine a likely range of future SI outcomes. Control protocols determine the specifics of how SI forecasts are used to select insulin treatments.

#### 2.3.1 STAR-NICU protocol

The 50<sup>th</sup> percentile of likely SI outcomes is used to determine the 50<sup>th</sup> percentile of BG outcomes for defined insulin and nutrition inputs. An insulin rate is chosen such that the 50<sup>th</sup> percentile of BG outcomes is placed on a median target of 6.0 mmol/L and the 5<sup>th</sup> percentile of likely outcomes is greater than 4.0 mmol/L (Le Compte et al., 2009). As added protection against noise or mis-measurement, the rate of change of insulin is limited to a maximum increase of 0.03 U/kg/hr per treatment.

#### 2.3.2 STAR-GRYPHON protocol

The 95<sup>th</sup> percentile of likely SI outcomes is used to determine the 5<sup>th</sup> percentile of BG outcomes for defined insulin and nutrition inputs. STAR-GRYPHON balances risk by choosing an insulin rate such that the 5<sup>th</sup> percentile of BG

outcomes is placed within tolerance of a lower target of 4.4 mmol/L, thus ensuring 95% of likely BG outcomes are above this target.

For safety and robustness, if current BG is greater than 9 mmol/L, insulin infusion can increase by up to 0.06 U/kg/hr, while if BG is between 6-9 mmol/L it can increase by up to 0.03 U/kg/hr, and if  $BG < 6$  mmol/L it can only increase by up to 0.02 U/kg/hr. Insulin infusion rates are allowed to decrease or be turned off at any time. The basis of this protocol is published elsewhere (Dickson et al., 2013).

### 2.4 Analysis of results

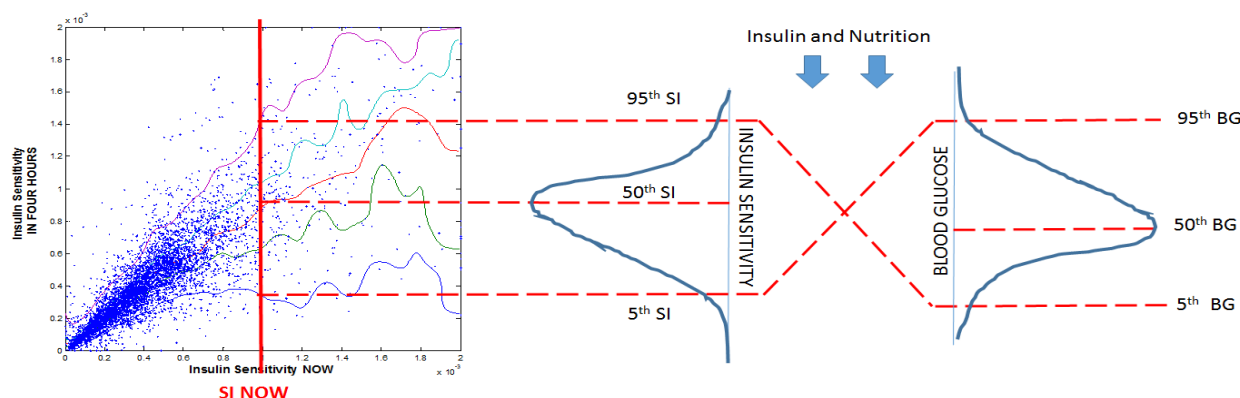
Re-sampled statistics use the model generated BG profile and hourly re-sampling to estimate BG behaviour between measurements. In instances where the measurement interval is different, re-sampled statistics allow a fairer comparison between the groups, as well as an indication of glycaemic behaviour between measurements.

Safety is reflected by the number of patients with a severe hypoglycaemic event ( $BG < 2.6$  mmol/L) and minor hypoglycaemia ( $BG < 4.0$  mmol/L). Performance is determined by the percentage time in the 4.0-8.0 mmol/L target band, and minimisation of hyperglycaemia ( $BG > 10.0$  mmol/L).

## 3.0 RESULTS

40 premature infants totalling 61 STAR-NICU episodes from August 2008 to December 2012. Of these patients, 8 were short term pilot trials and the rest from long term trials or received STAR-NICU as a clinical standard of care. 22 STAR-NICU patients have been reported previously (Le Compte et al., 2012). In 2013, 4 patients totalling 5 episodes received insulin under STAR-GRYPHON. In addition, 22 retrospective patients treated prior to August 2008 using clinical titration of insulin provide a baseline comparison. Clinical results are given in Table 1.

Median BG was lower for STAR-NICU and STAR-GRYPHON compared to retrospective data ( $p < 0.005$ , Mann-Witney U test). The median BG between STAR-NICU and STAR-GRYPHON was similar ( $p = 0.1$ , Mann-Witney U test). Cumulative distributions of BG in Figure 3 are significantly different ( $P < 0.005$ , Kolmogorov-Smirnov test), and are steeper for STAR-NICU and STAR-GRYPHON in



**Figure 2: Using stochastic models to forecast likely changes in insulin sensitivity (SI), given its current value, and thus blood glucose (BG) outcomes for given insulin and nutrition interventions**

comparison to retrospective data. Notably, STAR-GRYPHON has much less BG<4.9 mmol/L.

STAR-NICU protocol saw an absolute 18% increase in re-sampled BG in band (14% of BG measurements) and the percentage of hyperglycaemic measurements roughly halved. The newer STAR-GRYPHON protocol and implementation has seen the resampled BG in the target band rise to 87% (83% of all BG measures), with no incident of moderate to severe hypoglycaemia. This reflects a 17% increase BG in the target band in comparison to STAR-NICU, and a 35% increase with respect to retrospective data.

#### 4.0 DISCUSSION

The STAR-NICU protocol increased the percentage of BG measurements within the target band of 4.0 – 8.0 mmol/L in comparison to retrospective data, indicating achievement of tighter glycaemic control. This result was predominantly due to the reduction of hyperglycaemia and lowering of the median patient BG, and results across an increased cohort of patients reflect those of early published pilot trials (Le Compte et al., 2012). However, the overall shift of BG and tightening of control seen in Figure 3 resulted in an increase in the incidence of mild hypoglycaemia (BG<4.0 mmol/L). In addition, there was an increase in the number of patients with an incidence of BG<2.6 mmol/L.

STAR-GRYPHON has shown no moderate or severe hypoglycaemia, for similar median BG levels, and much higher time in the target band in comparison to the pilot STAR-NICU trials. Figure 3 shows a significantly steeper cumulative distribution of BG, indicating much tighter glycaemic control than either retrospective clinical data or STAR-NICU could achieve. This is reflected in the absolute 35% and 17% increase performance compared with retrospective and STAR-NICU clinical data respectively. Although there are only 5 patient data sets, this trend is expected to continue, due to the additional safeguards allowing higher rates of change in insulin at high BG, and lower limits on the amount by which insulin can increase for BG<6 mmol/L.

Glucose delivery was lower in STAR-GRYPHON. Lower glucose delivery does lower the insulin required, and thus lowers the risk and can aid in tightening control. However, in simulation STAR has been shown to tighten control for the same glucose inputs (Dickson et al., 2013), so the lower glucose rate alone fails to account for the increase in performance. Insulin delivery has increased slightly from retrospective data, indicating that increased tightness and safety of control is due to more effective use of insulin, as STAR takes into account patient SI. Additionally, all glucose delivery is clinically determined, and is thus not touched by STAR

The basis of the development and optimisation of the STAR-GRYPHON protocol has been previously published (Dickson et al., 2013), though small changes to stochastic forecasting methods improved control since then. STAR GRYPHON clinical results show improved safety and reduced hyperglycaemia than previously published, in line with more recent simulation. The median BG of 6.7 [6.1-7.5] is slightly

higher than the 6.6 [5.5–8.5] mmol/L predicted by simulation. Simulation based on the retrospective and STAR-NICU dataset indicates that STAR-GRYPHON would improve on clinical data to date and is likely to continue to provide safe and effective control in the future.

The benefits of insulin therapy to promote increased glucose tolerance and weight gain has been well reported (Collins et al., 1991, Pollak et al., 1978, Ostertag et al., 1986, Kanarek et al., 1991, Thabet et al., 2003, Meetze et al., 1998, Binder et al., 1989). However, these studies tend to report very few statistics with respect to the quality of glycaemic control. Rates of hypoglycaemia, when discussed, are often reported

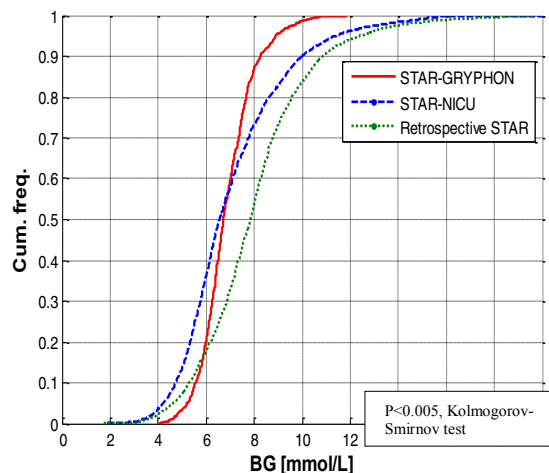


Figure 3: Whole cohort blood glucose (BG) cumulative distributions

Table 1: Cohort clinical and glycaemic statistics. Data are given as Median [Interquartile range].

	Retro-spective	STAR-NICU	STAR-GRYPHON
<b>n Patients (n male)</b>	22 (7)	40 (22)	4 (4)
<b>n Episodes</b>	25	62	5
<b>Gestational Age</b>	27 [25-27]	26 [25-29]	26 [26-27]
<b>Weight</b>	845	785	925
	[800-900]	[635-950]	[810-1160]
<b>Post Natal Age</b>	-	3 [1-7]	1 [1-2]
<b>Total Hours</b>	3098	5014	457
<b>Number of BG measurements</b>	943	1632	123
<b>Measurement interval</b>	3.2	3.3	4.0
	[2.6 - 3.9]	[2.7 - 3.8]	[3.8 - 4.0]
<b>Insulin rate [IQR] (U/kg/hr)</b>	0.03	0.04	0.04
	[0.02-0.06]	[0.02-0.08]	[0.03-0.06]
<b>Glucose rate [IQR] (mg/kg/min)</b>	8.1	7.4	7.2
	[5.7 - 9.7]	[5.2 - 8.6]	[6.4 - 8.2]
<i>Hourly re-sampled statistics</i>			
<b>Median BG</b>	7.8	6.6	6.7
	[6.6 - 9.1]	[5.5 - 8.2]	[6.1 - 7.5]
<b>% BG within 4.0 - 8.0 mmol/L</b>	51.9	69.8	87.2
<b>% BG&gt;10 mmol/L</b>	16.3	9.9	1.5
<b>% BG&lt;4.0 mmol/L</b>	2.1	3.5	0
<b>% BG&lt;3.0 mmol/L</b>	0.3	0.4	0
<b>% BG&lt;2.6 mmol/L</b>	0.1	0.2	0
<b>Num episodes with BG &lt;2.6</b>	1	8	0

as the percentage of all BG measures taken, and are typically less than 1% BG<2.2 or 2.6 mmol/L. Further, target ranges and definitions of hyper- and hypo- glycaemia vary across centres (Alsweiler et al., 2007) and between studies. Thus, very little literature is available with which these STAR glycaemic control results can be compared, and such difficulties can be compounded by differences in practice and definition.

In a randomised control trial (HINT trial) of tight glycaemic control (TGC) and standard of care Alsweiler and colleagues (Alsweiler et al., 2012) questioned whether the benefits of TGC are outweighed by the risks of hypoglycaemia. A doubling of the number of incidences of hypoglycaemia (58% of infants with one or more BG<2.6 mmol/L in the TGC group compared with 27% in the control group) is reported, despite the fact that around a third of the control group ended up being treated with insulin as well (Alsweiler et al., 2012). Beardsall and colleagues (Beardsall et al., 2008) report a high rate of hypoglycaemia (defined as BG<2.6 mmol/L for more than 60 min when measured by continuous glucose monitor (CGM)), with 29% of infants receiving early insulin therapy experiencing one or more hypoglycaemic events compared with 17% in the control group. In a study comparing insulin therapy between ELBW and LBW infants, Ng and colleagues (Ng et al., 2005) report that 15% of ELBW and 11% of LBW infants had BG<2.6 mmol/L during their study.

The original STAR-NICU protocol shows occurrence of the number of patients with a severe hypoglycaemic event (8/61 or 13% of all episodes), a result which is much less than the HINT and NIRTURE studies (Alsweiler et al., 2012, Beardsall et al., 2007), and similar to that reported by Ng, who had much higher BG levels. STAR-GRYPHON to date has shown no severe hypoglycaemic events, and no BG<4.0 mmol/L.

The median BG from neonatal STAR was 6.6 [5.5 - 8.2] mmol/L for STAR-NICU and 6.7 [ 6.1 - 7.5] for STAR-GRYPHON, which is similar to the 6.2±1.4 mmol/L seen in the early insulin group of the NIRTURE trial, and slightly higher than the TGC group median of mean daily glucose measure 5.8 [4.8-6.7] mmol/L. It should be noted that the glycaemic control statistics are only reported for study days 2-7 in the NIRTURE trial. Comparison to Ng is made difficult as only the median [range] BG during insulin therapy is reported (12 [6-24] mmol/L in the ELBW cohort, and 11 [7-19] mmol/L in the LBW cohort), which are much higher than those of STAR.

Hyperglycaemia is associated with increased mortality and morbidity (Alaedeem et al., 2006, Bistran, 2001, Blanco et al., 2006, Hall et al., 2004, Hays et al., 2006, Kao et al., 2006). Thus, reduction of BG levels is expected to reduce mortality (Hays et al., 2006, Hall et al., 2004, Kao et al., 2006), morbidity, and hospital length of stay (Hays et al., 2006, Hall et al., 2004, Alaedeem et al., 2006). As such, the benefits extend beyond the infant and their kin, increasing hospital resource availability and reducing overall clinical workload.

Further studies examining the benefits of TGC need to focus on first achieving TGC, and then examining the outcomes. The results presented indicate that the STAR protocols can safely and effectively achieve TGC control in the extremely low birth weight neonate. This TGC control protocol has been clinically implemented, and is now a standard of care at Christchurch Women's Hospital.

## 5.0 CONCLUSIONS

STAR is a model based glycaemic control system for extremely premature preterm infants. It has successfully been implemented as a standard of care at Christchurch Women's Hospital, New Zealand, and the original implementation halved hyperglycaemia and increased measurements in the targeted band by 14%. Recent implementation of the optimised STAR-GRYPHON protocol has resulted in 83% of measurements in the target band (35% better than retrospective data and 17% better than original STAR NICU protocols), and no incidence of BG<4.0 mmol/L. Comparison with results from literature is made difficult by lack of reported glycaemic control statistics, but STAR seems to achieve better or comparable control to published studies with much lesser incidence of hypoglycaemia. Further studies need to focus on achieving tight glycaemic control to fully determine the long term impact on outcome and benefits to the NICU cohorts.

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