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# Fifteen Years of Model-Based Glycaemic Control in Preterm Neonates: Safety, Performance, and Evolution of Insulin Sensitivity and Cohort Characteristics

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# Abstract

**Objective**: Glycaemic control (GC) in the neonatal intensive care unit (NICU) is debated due to significantly increased risk of hypoglycaemia. This study reviews the safety and performance of 15-years of model-based GC in the Christchurch Women's Hospital NICU.

**Study Design**: Retrospective and model-based protocols (STAR; STAR-GRYPHON) are compared in 2-3 year epochs, and overall. Safety is assessed via severe hypoglycaemia, and performance via time in 4.0-8.0mmol/L. Cohort evolution is assessed by the evolution of model-based insulin sensitivity (SI), birthweight (BW), and gestational age (GA).

**Results**: Model-based control was safer than Retrospective sliding scale control with better performance. Performance declined over time with increasing low SI values concomitant with lower BW and GA.

**Conclusion**: STAR-GRYPHON GC is safe and effective. Performance is increasingly limited by cohort evolution creating trade-offs between increasing insulin dose and risk required to achieve normoglycaemia in the face of demographically decreasing gestational age and birthweight.


# 1.0 Introduction

Hyperglycaemia can be common in pre-term infants (1, 2) due to stress and prematurity (3–5). Gycaemic control (GC) and insulin therapy in the neonatal intensive care unit (NICU) tries to normalise blood glucose (BG) levels to mitigate the negative impacts of hyperglycaemia (1, 6, 7), while also avoiding hypoglycaemia and its risks (8). GC can improve glucose tolerance and increase post-natal weight gain (e.g. (9–12)). However, clinically, it often results in excessive protocol-induced hypoglycaemia (13, 14), largely due to their significant metabolic variability compared to adult ICU patients (15, 16).

STAR-GRYPHON is a model-based GC protocol for hyperglycaemic pre-term infants which has provided good performance with minimal hypoglycaemia over several years (17–20). It uses risk-based target-to-risk dosing to directly manage inter- and intra- patient variability in guiding care (18, 21–23). The underlying physiological digital twin model employed is clinically well-validated over 15 years (24–26). A similar foundation model is used successfully in adult ICU GC for almost 20 years (27, 28). However, while the protocol and model have been unchanged for the past 13 years, GC performance and safety has varied and degraded slightly from initial results despite consistent compliance (17).

This study examines the interaction of GC performance for the past 20 years from a retrospective set of data used to design the first digital twin models through the two main iterations of this model-based GC. Performance over this period is assessed against changes in the patient demographics and model-based metrics used to personalise and optimise care. The overall goal is to assess the impact of changes in cohorts on performance and thus draw specific lessons for the future of care.

# 2.0 Methods

### *2.1 Study population*

De-identified glycaemic control data from Christchurch Women's Hospital NICU is retrospectively analysed from 2005-2023. Data includes BG measurements, insulin and glucose infusion rates, and patient demographics (GA (gestational age), PNA (postnatal age), and birthweight). There are 3 cohorts based on GC protocol: **1**) 'Retrospective' who received insulin under a sliding-scale paper-based protocol (2005-2008); **2**) STAR-1 (2009-2012) treated with a first iteration of a 'STAR' (**S**tochastic **TAR**geted) computerised protocol adapted to neonates (20); and **3**) STAR-GRYPHON (2013-2023) treated with the computerised STAR-GRYPHON (**S**tochastic **TAR**geted **G**lucose **R**egulation s**Y**stem to **P**revent **H**yper- and hyp**O**-glycaemia in **N**eonates) protocol developed from STAR using an enhanced model (17, 18, 29) as a standard of care.

Retrospective data was collected from hospital records to develop and test the STAR-1 pilot and later the STAR-GRYPHON protocols. Insulin rates were guided by a sliding scale (19, 20), where recommendations were often modified, with the clinical goal of maintaining BG within 5.0–8.0mmol/L and avoiding hypoglycaemia. All patient episodes are longer than 12 hours duration.

STAR-1 and STAR-GRYPHON data were automatically collected by the computerised protocol and de-identified for audit. This analysis discarded treatment episodes with fewer than 5 BG measurements or duration shorter than 12-hours. STAR-GRYPHON patients may have more than 1 treatment episode where insulin infusions are restarted more than 12-hours since prior use, where STAR and Retrospective cohorts are single episode per patient.

Ethics approval and consent to participate**:** De-identified clinical data were retrospectively analysed as part of a registered clinical data audit with the Women's and Children's Safety and Quality Audit Committee, Christchurch Women's Hospital, Christchurch, New Zealand (August 2017). STAR and STAR-GRYPHON were used as standard clinical care, and no research-specific intervention was undertaken. Thus, formal research ethics approval and individual informed consent to participate were not required for this retrospective audit of de-identified standard-of-care data. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### *2.2 Computerised insulin dosing protocols*

The computerised STAR-1 and STAR-GRYPHON protocols both utilise similar methodology. A physiological digital-twin model of glucose-insulin action is used with BG measurements to identify the value of current patient insulin sensitivity. BG outcomes are then predicted across possible insulin doses. Nutrition is left to clinical goals and not altered for control unlike the adult ICU case (17, 20). Forward prediction utilises stochastic modelling to determine probability ranges for changes in insulin sensitivity over time (21, 22, 29), which are used with the physiological model (26) to estimate BG outcome ranges for different insulin and clinically specified nutrition interventions. Thus, these

computerised protocols titrate insulin to current patient metabolic condition, and likely changes in this insulin sensitivity over the next 2-4 hours. This risk-based approach (23, 30), minimises risk of BG<4.0mmol/L to <5% accounting for variability over time between BG measures (29). The overall computerised protocol calculation process is given in **Figure 1**.

STAR-1 and STAR-GRYPHON have different underlying models. STAR-GRYPHON uses a more detailed physiological model (26), and its stochastic model is built from the greater combined Retrospective and STAR-1 data (22, 29), vs. just the Retrospective data for STAR-1 (21). Compared to the adult case (28), the models are tailored to reflect the metabolic physiology of preterm infants (26). Further details on the physiological and stochastic models are in prior literature (18, 22, 26, 29, 31).

Insulin infusions are initiated for 2 consecutive BG≥10.0mmol/L per clinical protocol. Insulin is diluted to a concentration of (5 x weight (kg)) U made up in 20mL saline, so a 0.05U/kg/hr infusion rate is 0.2mL/hr. It is initiated by a 2-3hour 0.05U/kg/hr starting insulin infusion rate and the next BG measurement initiates model-based control. Every BG measurement yields recommendations for 2, 3 and 4-hour treatment options, where the clinician chooses the interval based on clinical equipoise.

### *2.3 Clinical procedures*

Blood samples are taken from a central umbilical arterial line, if available, or capillary heel pricks. BG is determined using a Bayer 850 blood gas analyser (Bayer AG, Germany). Insulin tubing is pre-soaked in insulin solution for 15 minutes to prime the line and minimise insulin losses due to adsorption (32). Insulin infusions are delivered via the same line as dextrose fluids, with a resolution of 0.01U/kg/hr.

All nutrition and glucose intake is clinically determined independent of STAR and STAR-GRYPHON, but past and (intended/planned) future glucose infusion rates are input for model-based calculations. Total glucose delivery is typically 6-8mg/kg/min, with total parenteral nutrition (TPN, 10% glucose) as the largest contributor. Medications, such as dobutamine and morphine, may be infused with 5% dextrose or saline solutions. Enteral boluses of expressed breast milk (EBM) or milk formula are clinically used as soon as available, starting at 0.5mL every 4-hours, with increasing volume and frequency as tolerated. All these inputs are included in the model and recommendations.

### *2.4 Analyses*

Previous work showed decreasing insulin sensitivity in recent years in insulin-treated adult ICU patients (33). Thus, this analysis aimed to answer two questions:

1. Has glycaemic control safety and/or performance changed over time?
2. Have insulin sensitivity distributions at the cohort level changed over time?

The overall study covers 15-years of model-based GC in this NICU, and is the first long-term audit/analysis of this type of intervention to the authors' knowledge. The study is reported in accord with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Model-based Insulin sensitivity is fit hourly from clinical data (34). All episodes from all cohorts are analysed with the model of (26) to produce a data set including: all clinical glucose/insulin inputs; all clinical BG measurements; hourly insulin sensitivity values; and minute-wise BG profiles between clinical BG measurements.

Glycaemic control performance is assessed in terms of safety from hypoglycaemia (mild: %BG<4.0mmol/L; severe: %BG<2.6mmol/L), time-in-target range (4.4–8.0mmol/L), and minimisation of hyperglycaemia (%BG>8.0 and 10.0mmol/L). These metrics are sampled hourly from model-fit BG using linear interpolation (35) for a fairer comparison between groups with varying measurement intervals. This analysis is not designed or powered to examine morbidity and mortality outcomes.

Statistical analyses were carried out using Matlab (Mathworks, United States). Data are presented as median and interquartile range (IQR) unless otherwise specified. Cohorts are arranged into sub-groups according to cohort and year intervals as: 2005-2008 (Retrospective cohort), 2009-2012 (STAR-1), 2013-2014, 2015-2016, 2017-2018, 2021-2023. No data was collected over the 2019-2020 period due to an unnoticed software issue with data storage. The Retrospective and STAR-1 cohorts provide a pre-STAR-GRYPHON baselines against which 2-yearly STAR-GRYPHON results are compared. Two-yearly intervals are used to provide a similar period to the 2-3 year Retrospective and STAR-1 periods, while allowing enough resolution to track changes in cohort response to care.

Statistical comparisons of demographic data (weight, PNA, GA) were performed using a two-tailed student's t-test. Much greater data density of hourly SI measures across cohorts can result in over-sensitivity of statistical tests to small changes in data distribution (36). Thus, boot-strapped statistics are used, where data from each of any two cohorts (A, B) was bootstrapped with replacement 10,000 times to generate 10,000 paired samples for A and B, of length n=minimum(length(A),length(B)). For a comparison of data medians, the median difference of each bootstrapped sample pair ($A_i - B_i$) was computed, and the median [confidence interval (CI)] of this median difference is presented. Where the CI does not cross zero, samples A and B are statistically different to $p = (1 - CI)$ (37). As multiple comparisons are made between the 6-year groupings (total, 15 comparisons), a Bonferroni correction is used, giving a corrected p-value for statistical significance was taken as $p \leq \frac{0.05}{15} = 0.0033$ (CI: 99.7), which is lower than the $p \leq 0.05$ commonly used in medical literature.

# 3.0 Results

Summary demographic data and results are in **Table 1**. From 2013-2023 95 glycaemic control 'episodes' using STAR-GRYPHON were recorded. Software storage failure meant 2019-2020 STAR-GRYPHON data was not saved. They are compared to 25 retrospective patients from 2005–2008, and 53 STAR-1 pilot patients in 2009-2012 (20).

STAR-1 improved GC performance within the 4.4-8.0mmol/L range from 51.9% to 69.8%, and peaked in the 2013-2014 period with 77.3% time in range. Performance gains were primarily achieved by reducing

hyperglycaemia (BG>8.0 and 10.0mmol/L), though STAR-1 also increased %BG<4.0mmol/L from 2.1% to 3.6% and the number of episodes of BG<2.6mmol/L. STAR-GRYPHON consistently improved safety across all years, with %BG< 4.0mmol/L ranging from 0.6-0.9%. STAR-GRYPHON consistently showed higher %BG in the 4.4-8.0mmol/L range compared to Retrospective data, though performance decreased gently from 2015. Overall, STAR-GRYPHON improved time-in-target range, while improving safety in %BG<4.0mmol/L and number of episodes of severe hypoglycaemia (1 in 33 for GRYPHON vs 1 in 25 for Retrospective).

Changes in STAR-GRYPHON performance may be linked to underlying demographic changes, as shown in **Figure 2**. **Figure 2** shows overall lower birthweight of STAR-GRYPHON treated infants from 2015 onwards, with lowest cohort birthweights observed in the 2021-2023 period. This difference is statistically significant at the $p<0.05$ threshold if the 2021-2023 period is compared to the 2013-2014 and retrospective data periods ($p=0.02$ and $p=0.01$). No statistically significant trend in infant gestational or postnatal age is observed over this period, although both decline at median value.

Concurrently, **Figure 2** and **Table 2** show statistically significant decreasing SI over time, with almost all year group comparisons significant to a multiple-comparison Bonferroni corrected threshold of $p<0.003$. Only the Retrospective and STAR-1 cohorts are clinically equivalent to < 15% difference in insulin sensitivity. Insulin sensitivity changes allow comparisons year-to-year independent of clinical variables, such as starting BG, and decreasing insulin sensitivity directly indicates more insulin was required to achieve similar BG reductions. Concomitantly, **Table 1** shows increasing median insulin doses across the 2005-2023 period in support of this point, despite similar overall reductions in nutrition administration. Thus, patients treated using STAR-GRYPHON were overall becoming increasingly insulin resistant over time, which is generally linked to being more critically ill (1, 2) and metabolic prematurity (3-5). This increased insulin resistance explains decreasing GC performance in the 4.4-8.0mmol/L range from 2013-2023, with the concomitantly increasing hyperglycaemia in %BG>8.0 and 10.0mmol/L (light and moderate hyperglycaemia), particularly when considering maximum insulin infusion rates and their increases are both limited by GRYPHON for safety.

**Figures 3a-b** show illustrative examples of good glycaemic control, where BG is brought within range and rising insulin sensitivity results in gradually decreasing insulin infusion rate. In contrast, **Figures 3c-f** show more complex cases, which tend to start with 40+ hours of persistent, light hyperglycaemia despite increasing insulin infusion rates. These latter cases are significant contributors to the drop in %BG in target range, and increased %BG>10.0, from 2017-2023. **Figures 3e-f** also show glycaemic variability, with underlying insulin sensitivity variability resulting in BG variability. In all these examples, no significant change in nutrition rate or EBM size/frequency is observed, eliminating it as a cause. Overall, increasing insulin resistance leading to persistent early hyperglycaemia appears to be the primary driver of reduced performance in 2017-2023 in **Table 1**.

**Table 1**: Cohort demographic data and glycaemic control safety and performance for all cohorts of GRYPHON, STAR pilot and the Retrospective cohort. There is also a column for “All” GRYPHON results on

the right column. There are also overall and hourly resample statistics as noted, where whole cohort raw statistics cover direct measurements and all safety and performance are hourly resampled for even comparison. Insulin sensitivity data is in **Table 2**.

| | Retro | STAR pilot | GRYPHON | | | | |
|---|---|---|---|---|---|---|---|
| | **2005-2008** | **2009-2012** | **2013-2014** | **2015-2016** | **2017-2018** | **2021-2023** | **All GRYPHON** |
| **Number (N)** | 25 | 53 | 20 | 26 | 34 | 15 | 95 |
| **GA (weeks)** | 26.6 [25.4-27.1] | 25.9 [25.0-28.9] | 26.4 [26.1-27.3] | 26.5 [25.0-29.0] | 25.1 [24.4-27.6] | 25.9 [23.9-26.9] | 26.1 [24.9–27.4] |
| **PNA (days)** | 4 [2-7] | 3.5 [1-8] | 3.5 [3-5.5] | 2.0 [1-7] | 3.5 [2-15] | 3 [1-6.5] | 3 [2–9] |
| **Birth Weight (g)** | 845 [800-904] | 860 [635-985] | 932 [820-987] | 770 [670-970] | 750 [710-810] | 654 [592-719] | 760 [663–936] |
| ***Glycaemic Control–Whole cohort statistics*** | | | | | | | |
| **N hours on GC** | 3098 | 4900 | 1073 | 1852 | 2716 | 864 | 6505 |
| **#BG measurements** | 943 | 1525 | 300 | 495 | 711 | 242 | 1748 |
| **Measurement interval (hours)** | 3.2 [2.6-3.9] | 3.3 [2.9-3.9] | 3.8 [3.1-4.0] | 3.9 [3.4-4.0] | 4.0 [3.6-4.0] | 4.0 [3.5-4.0] | 4.0 [3.8-4.0] |
| **Starting BG (mmol/L)** | 10.4 [7.2-12.4] | 10.5 [8.8-11.6] | 9.2 [7.5-11.1] | 10.6 [9.9-12.5] | 11.3 [9.0-13.6] | 10.4 [7.6-13.3] | 10.8 [8.9-12.5] |
| ***Hourly resampled glucose statistics*** | | | | | | | |
| **BG (mmol/L)** | 7.9 [6.6-9.2] | 6.6 [5.6-8.2] | 7.1 [6.2-8.3] | 7.2 [6.1-8.6] | 7.6 [6.4-9.1] | 7.6 [6.4-9.0] | 7.3 [6.3–8.8] |
| **%BG in 4.4-8.0mmol/L*** | 51.9 | 69.8 | 77.3 | 67.6 | 58.7 | 61.9 | 64.7 |
| **%BG >10.0mmol/L*** | 16.3 | 9.7 | 5.8 | 7.7 | 13.6 | 10.9 | 10.3 |
| **%BG <4.0mmol/L*** | 2.1 | 3.6 | 0.6 | 0.6 | 0.9 | 0.7 | 0.7 |
| **%BG <2.6mmol/L*** | 0.1 | 0.2 | 0.0 | 0.1 | 0.1 | 0.0 | 0.1 |
| **# GC episodes with BG<2.6** | 1 | 5 | 0 | 1 | 2 | 0 | 3 |
| **Hourly Insulin (U/kg/hr)** | 0.03 [0.02-0.06] | 0.04 [0.01-0.08] | 0.05 [0.04-0.07] | 0.08 [0.04-0.10] | 0.08 [0.05-0.11] | 0.07 [0.05-0.10] | 0.07 [0.04-0.10] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Nutrition (mg/kg/min)** | 8.1 [5.7-9.7] | 7.3 [5.1-8.5] | 7.7 [7.1-8.7] | 7.7 [5.8-8.9] | 6.8 [4.2-8.2] | 5.9 [4.3-7.5] | 7.2 [5.3-8.5] |

**Table 2:** Comparison of bootstrapped insulin sensitivity (SI) distributions across epochs. As comparisons are symmetric, the upper triangle presents the median [99.7$^{th}$ CI, confidence interval with Bonferroni correction] percentage difference in SI, while the lower triangle gives statistical interpretation. CI ranges which do not cross zero are statistically significant ($p < 0.0033$ corrected).

| | | **Retro** | **STAR 1** | **GRYPHON** | | | |
|---|---|---|---|---|---|---|---|
| | | **2005-2008** | **2009-2012** | **2013-2014** | **2015-2016** | **2017-2018** | **2021-2023** |
| **Retro** | **2005-2008** | | 5.8 [-0.9-12.4] | 18.9 [13.3-24.7] | 59.2 [53.4-65.4] | 85.8 [79.6-91.6] | 68.2 [58.6-83.0] |
| **STAR 1** | **2009-2012** | **ó** | | 13.2 [6.5-20.3] | 53.8 [47.3-61.1] | 81.1 [74.4-87.3] | 63.5 [52.3-79.0] |
| **GRYPHON** | **2013-2014** | **P<0.0033** | **P<0.0033** | | 41.4 [35.4-48.7] | 69.7 [62.8-76.0] | 51.0 [43.0-65.6] |
| | **2015-2016** | **P<0.0033** | **P<0.0033** | **P<0.0033** | | 30.5 [21.9-37.9] | 10.2 [-3.2-27.5] |
| | **2017-2018** | **P<0.0033** | **P<0.0033** | **P<0.0033** | **P<0.0033** | | -20.0 [-32.5--0.8] |
| | **2021-2023** | **P<0.0033** | **P<0.0033** | **P<0.0033** | | | |

Lower triangle bootstrapped p-values are relative to a corrected threshold of $p<0.0033$, and **ó** highlights equivalency to %ΔSI<+/-15%. Note, it is theoretically possible to be statistically different but clinically equivalent.

# 4.0 Discussion

This analysis examined time progression of glycaemic control performance over 10+ years of experience with a computerised glycaemic control protocol to guide insulin therapy in a neonatal intensive care unit. It was found the computerised glycaemic control protocol STAR-GRYPHON did not increase the incidence of hypoglycaemia relative to a potentially less critically ill Retrospective cohort, where the declining values of SI and BW in particular over time are markers of more complex and critically ill infants. Glycaemic control performance, as reflected in the %BG within the targeted 4.0-

8.0mmol/L range and %BG>10.0mmol/L, improved relative to the retrospective baseline (52% to a peak of 77% BG in range). However, this performance decreased over time due to increasing incidence of persistent early hyperglycaemia, despite increasing, and often high, insulin infusion rates. Statistically significant reductions in insulin sensitivity were observed over this period indicating a more counter-regulated and critically ill cohort.

While %BG>10.0mmol/L is overall highest in the Retrospective cohort (16%), it increases from its minimum of 5.8% in 2013-2014 to 13.6% in 2017-2018 and 10.9% in 2021-2023. In part this increase can be attributed to higher starting BG (**Table 1**). However, this increase in hyperglycaemia, and decreased %BG in the target range, follows a concomitant statistically significant decrease in insulin sensitivity over this period, suggesting an underlying change in the cohort metabolic state. Hence, this consistent decrease in insulin sensitivity suggests performance reductions are not predominantly driven by clinical changes, such as starting BG or glucose intake rate, but instead by changing patient condition.

For safety, GRYPHON limits insulin infusion rates based on clinician choice. In adults, insulin 'effect,' or insulin-mediated glucose uptake, saturates (at ~6-8 U/hr (38-40)) at 0.08-0.13 U/kg for a 60-70 kg adult. Farrag et al (3) show no saturation in pre-term infants up to ~0.24 U/kg/hr. However, analysis and **Figure 3** show patterns consistent with insulin-effect saturation at ~0.2 U/kg/hr, with increased insulin rates leading to little or no change in glucose level. Thus, while not previously studied in detail due to the fragility of the cohort, the results show there may be an insulin saturation limit lower than previously reported. Hence, increasing insulin resistance is leading to insulin saturation and reduced performance, and may require restricting nutrition to achieve normoglycaemia in some cases.

These trends are matched in **Table 1** and **Figure 2** with decreasing birth weight (BW) despite no significant change in gestational age (GA). Thus, infants in the later cohorts were smaller without a corresponding significant shift in GA, suggesting birthweight may capture differences in patient condition or maturity not reflected by GA alone**.** However, low BW cohorts are the least desirable cases for reducing nutrition inputs to obtain better glycaemic control performance, indicating this level of persistent low hyperglycaemia may have to be tolerated. It should be noted nutrition restriction was previously preferred and has been the subject of several ongoing analyses and reviews (41-44). Hence, decreasing birthweight occurred concomitantly with decreasing insulin sensitivity, despite no significant change in gestational age, potentially reflecting changes in patient condition not captured by gestational age alone.

Overall, given these trends, STAR-GRYPHON appears to be a consistently safe and effective tool for glycaemic control. However, underlying low insulin sensitivity (increasing insulin resistance) is growing in this cohort, at least at this NICU, which impacts performance. If further glycaemic control performance were needed and/or reduced risk was desired, then nutrition inputs would have to be reduced, as is the case in adult ICU glycaemic control (16), which would be a consequential clinical choice between hypoglycaemic risk and performance at high insulin doses and risk of associated consequences. Thus,

increasing insulin resistance (decreasing insulin sensitivity) may require reconsidering nutritional intake for at least some infants in these cohorts if greater performance or reduced risk were desired.

One limitation of this study is the lack of detailed cohort diagnostics and data, which were not part of this performance and safety audit. These data could potentially provide other inputs to understanding the increased insulin resistance observed. It is also possible as medicine progresses and more infants who might previously be seen as unviable survive, these infants are making up a greater part of the hyperglycaemic cohort, influencing these results. Equally, improving antenatal care may be similarly "removing" an increasing number (of resulting) higher birthweight infants who thus "avoid" significant hyperglycaemia and the need for insulin. This study does not have the data to assess this possibility.

Further, insulin sensitivity is measured by a model-based metric, SI. This metric is imperfect, like all such model-based metrics. However, it is well-validated in adults against gold-standard euglycaemic, hyperinsulinemic clamps and intravenous glucose tolerance tests (45, 46). It is also used within a similar model-based format for 20-years in adult ICU glycaemic control with significant success in both performance and safety from hypoglycaemia (47). Finally, it has been used in adults to assess the impact of other treatments known to affect insulin sensitivity and shown good discriminatory power (e.g. (48-50)). Thus, it should suffice for this study given the magnitude of changes seen.

Last, this study is a single centre, observational study. The results may thus not generalise to other NICUs practicing glycaemic control, as cohorts, levels of antenatal care, and overall care approaches can vary significantly. However, the results show clear trends in insulin resistance and a matching trend in birthweight showing a clear linkage. They also show how insulin emerging patterns of insulin saturation effects, heretofore considered minor or irrelevant in this cohort, may need further examination to avoid insulin saturation and any increased risk to infants receiving insulin. Finally, the study spans 15 years as standard of care with consistent safety and control.

# 5.0 Conclusions

This study has tracked the progression of a model-based glycaemic control protocol for treating per-term infants in a neonatal intensive care unit. The main result shows the model-based approach used as standard of care has been safe and effective. Results also show a clearly increasing trend for lower birthweight infants and increased insulin resistance, the latter of which limits performance and leads to increased persistent light hyperglycaemia and potentially increased risk of hypoglycaemia due to the larger insulin doses required. Finally, they indicated patterns consistent with insulin-effect saturation in this cohort in contradiction to prior results in the field. Thus, the results start to characterise emerging trade-offs between care, and gestational age and birthweight, which should be considered in any insulin delivery to these cohorts, particularly as survival rates continue to improve for smaller and lower gestational age infants.

# Abbreviations

BG (Blood Glucose), BW (Birth Weight), GA (Gestational Age), GC (Glycaemic Control), GRYPHON (Glucose Regulation sYstem to Prevent Hyper- and hypO-glycaemia in Neonates), NICU (Neonatal Intensive Care Unit), STAR (Stochastic TARgeted)

# Declarations

**Ethics approval and consent to participate**: De-identified clinical data were retrospectively analysed as part of a registered clinical data audit with the Women's and Children's Safety and Quality Audit Committee, Christchurch Women's Hospital, Christchurch, New Zealand (August 2017). STAR and STAR-GRYPHON were used as standard clinical care, and no research-specific intervention was undertaken. Thus, formal research ethics approval and individual informed consent to participate were not required for this retrospective audit of de-identified standard-of-care data. The study was conducted in accordance with the principles of the Declaration of Helsinki

**Competing Interests**:There are no conflicts of interest to declare.

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# Figures

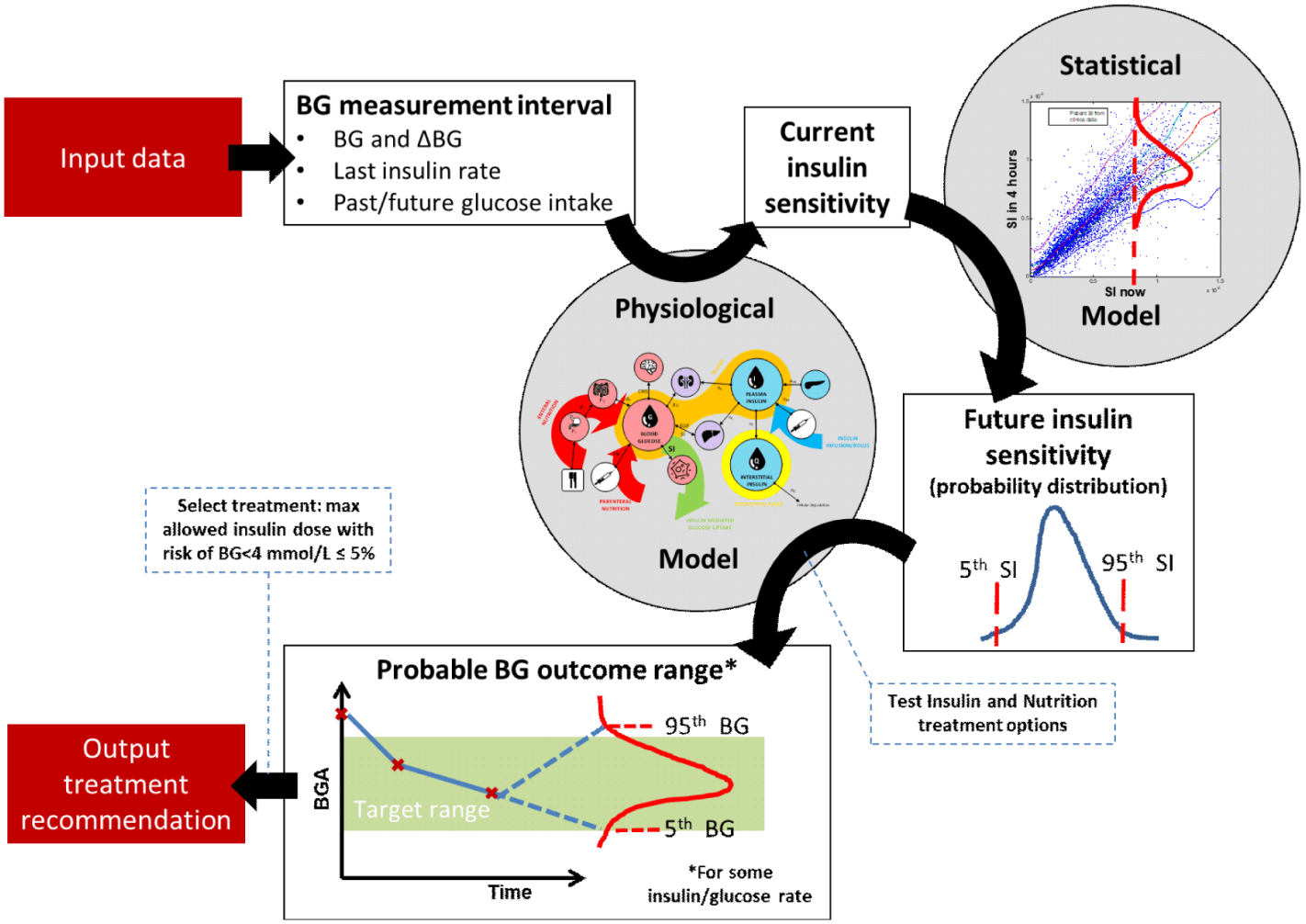



**Figure 1**: Computerised calculation process for the STAR and GRYPHON controllers. This process is completed each time a new insulin infusion rate is calculated when a new BG measurement is taken.

## Figure 1

Computerised calculation process for the STAR and GRYPHON controllers. This process is completed each time a new insulin infusion rate is calculated when a new BG measurement is taken.

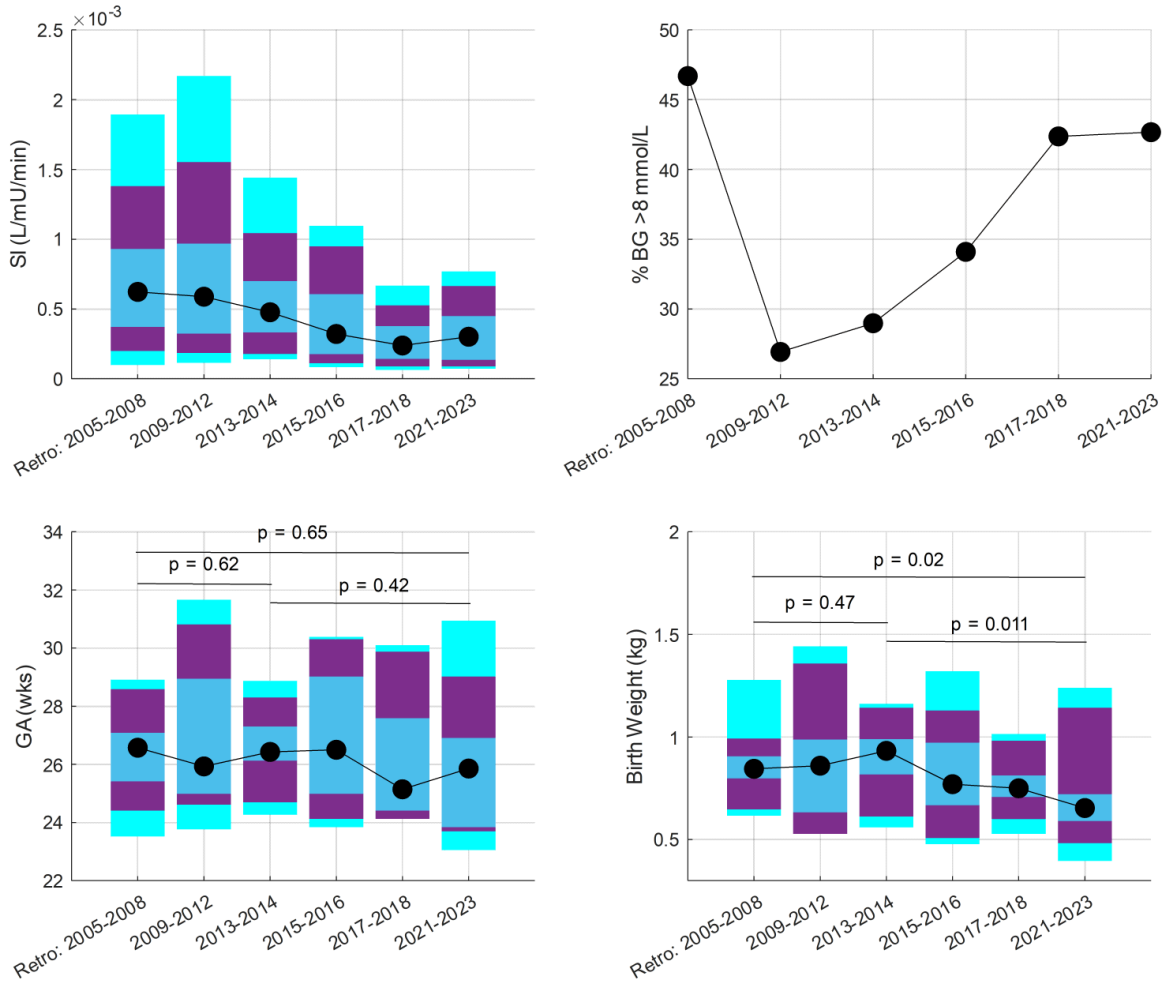



**Figure 2**: Timeline of demographic (GA, Birth Weight), hyperglycaemia (%BG>8.0mmol/L) and insulin sensitivity (SI) levels for each group and period. The solid dot is the median value, the dark blue middle bar is the inter-quartile range, the purple is the 90% range and light blue the full range.

## Figure 2

Timeline of demographic (GA, Birth Weight), hyperglycaemia (%BG>8.0mmol/L) and insulin sensitivity (SI) levels for each group and period. The solid dot is the median value, the dark blue middle bar is the inter-quartile range, the purple is the 90% range and light blue the full range.

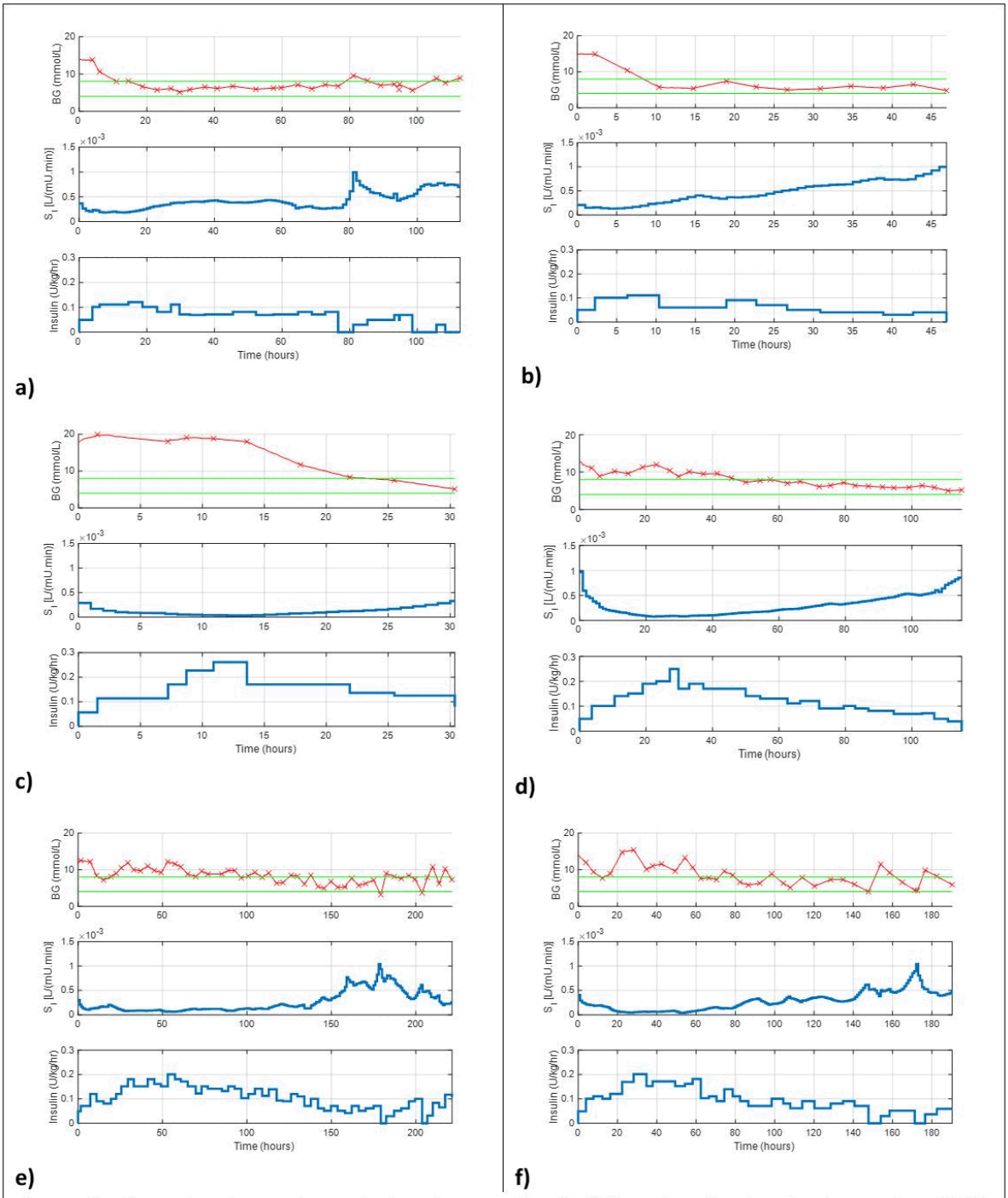



**Figure 3**: Example glycaemic control outcomes for 6 different patient episodes under STAR-GRYPHON from the years 2017-2023. SI is insulin sensitivity, and the insulin infusion rate is given in U/kg/hr. The BG plot shows the clinical BG measurements (x) and modelled BG between these measures (line), as well as the targeted BG range (green lines).

## Figure 3

Example glycaemic control outcomes for 6 different patient episodes under STAR-GRYPHON from the years 2017-2023. SI is insulin sensitivity, and the insulin infusion rate is given in U/kg/hr. The BG plot shows the clinical BG measurements (x) and modelled BG between these measures (line), as well as the targeted BG range (green lines).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEChecklistNICUGRYPHON15.docx