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NICE advice

The Space GlucoseControl system for managing blood-glucose in critically ill patients in intensive care

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Summary

Product summary and likely place in therapy	Effectiveness and safety
• The Space GlucoseControl system is intended to be used for controlling blood-glucose levels of critically ill patients in intensive care. • The Space GlucoseControl system would be used in place of manual protocols for planning the measurement of blood-glucose levels.	• Two prospective non-controlled cohort studies of the Space GlucoseControl system were identified (n=50). • Four randomised controlled trials and 1 non-controlled cohort study of the proprietary insulin-dosing computer algorithm used by the Space GlucoseControl system were identified. The 4 trials enrolled 34 to 120 people and the non-controlled study enrolled 20. • No evidence was available on the effectiveness of the Space GlucoseControl system in comparison with that of other glycaemic control protocols. No Space GlucoseControl system related severe adverse events were reported. • The comparative trials on the eMPC algorithm varied in terms of the standard glucose management protocols, the aspects of glucose control measured, and the findings. In general, the eMPC algorithm performed at least as well as the standard protocols for achieving and retaining glucose control. The eMPC algorithm seemed to have a higher risk of hypoglycaemia, but no severe hypoglycaemia was reported. Both the total time and the percentage of time in hyperglycaemia were reduced.

Technical factors	Cost and resource use
• The Space GlucoseControl system is an integrated computer-based decision support system that comprises 3 parts: a control unit; the computer algorithm used to calculate insulin dosing; and the insulin and nutrition infusion pumps.	• It costs £5,500 per unit to add the Space GlucoseControl module to an existing B. Braun system. • For intensive care units not already using the manufacturer's proprietary insulin and nutrition infusion pumps, it costs £12,300 to equip an intensive care bed with the full system. • No other consumables are needed.

Introduction

Dysglycaemia, or abnormal blood-glucose levels, has been estimated to affect up to 90% of patients in intensive care (De Block et al. 2008). Seriously ill patients often develop high blood-glucose levels because the body reacts to trauma or surgery by producing counter-regulatory stress hormones that cause insulin resistance. Around 215,000 adults in English NHS intensive care units had dysglycaemia in the year to March 2011. Of these, dysglycaemia followed surgical or anaesthetic procedures in 32.0% of cases and accidents in 10.1%. It is estimated that 7% of those patients with dysglycaemia in intensive care died before they were able to be discharged (Health and Social Care Information Centre 2012). Because dysglycaemia is associated with increased mortality (Dellinger et al. 2013; Jacobi et al. 2012), lowering blood-glucose levels is the focus of care for these patients. Insulin infusions are used to lower blood-glucose levels but they can cause glucose to drop below the healthy range, which also increases the risk of death. For this reason, glucose monitoring is needed to avoid hypoglycaemia as well as dysglycaemia (Jacobi et al. 2012).

Intensive care patients therefore benefit from regular blood-glucose monitoring; usually this is every 1 or 2 hours until glucose values and insulin infusion rates are stable, and every 4 hours thereafter to maintain control within specified limits (Dellinger et al. 2013). A number of care protocols have been developed to achieve this, and more recent computer-based predictive algorithms have shown better performance with fewer adverse effects than standard paper-based protocols (Horvorka et al. 2007; Hoekstra et al. 2009).

Blood-glucose control protocols need frequent blood sampling, and this increases the workload on nursing staff. Intermittent sampling may not always detect significant dysglycaemic events, so continuous glucose monitoring – and real-time updating of the protocols – may provide a better and safer means to manage blood-glucose levels in intensive care patients.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The Space GlucoseControl system is a Class IIb medical device. The manufacturer, B. Braun, received the first CE mark in June 2004. The most recent renewal was in May 2013.

Description

The Space GlucoseControl system comprises:

- a control unit with a touch-screen interface
- a computer running the eMPC algorithm to calculate the amount of insulin required for the next therapy interval
- the Space pump infusion system, which delivers the insulin dose, as well as providing enteral or parenteral nutrition.

The Space GlucoseControl device is a decision support system that calculates an optimum level of insulin dosing. It consists of 3 infusion pumps, 2 for enteral and parenteral nutrition, and 1 for insulin. The system automatically records information from the nutrition pumps including current status of infusion, bolus doses and carbohydrate intake. It

combines this information with manually-entered blood-glucose measurements, administered insulin dose and patient-specific data, such as previous response to insulin. A proprietary computer algorithm in the system, called the enhanced model predictive control (eMPC) algorithm, then predicts the future blood-glucose curve and calculates the best insulin dose rate to keep blood glucose within the range specified by the clinician responsible for the patient's care. The dose rate can be set to achieve 1 of 3 blood-glucose ranges: 4.4-6.1 mmol/l, 4.4-8.3 mmol/l or 5.6-8.9 mmol/l.

Based on the eMPC algorithm prediction, the Space GlucoseControl system calculates the time interval to the next blood-glucose measurement and gives an audio-visual alarm to alert nursing staff when it is due. The nurse then measures and enters the current blood glucose value, and the system suggests an appropriate insulin dose and time to next measurement. The advised insulin dose rate has to be confirmed, and is then set automatically at the pump. Changes in enteral and parenteral nutrition are communicated directly to the eMPC by the respective pumps, and automatically lead revised insulin rate and measurement interval if appropriate. The system uses a variable sampling time, which is event-based rather than time-based, in order to minimise the number of blood-glucose samples and reduce staff workload while maintaining the desired blood-glucose range. The system increases the time between sampling if measured blood glucose is in line with its prediction, and decreases the time if the prediction is less accurate (such as when the patient's health changes unexpectedly). The sampling interval can vary between 30 minutes and 4 hours. The operator of the Space GlucoseControl system can reduce the maximum sampling interval to 3 hours, 2 hours or 1 hour if needed.

Intended use

The Space GlucoseControl system is intended for the control of blood-glucose levels of patients in intensive care. The eMPC algorithm proposes an insulin dose rate calculated to keep the level within the normal glycaemic range, set by the clinician on a patient-by-patient basis.

Setting and intended user

The system is intended for use with critically ill patients in closely monitored environments, typically in hospital intensive care units. The manufacturer does not suggest that there are any patient groups in that setting for whom the system would not be suitable.

Current NHS options

Current protocols for blood-glucose control in critically ill patients vary between hospitals. These involve a combination of continuous insulin infusion and frequent blood-glucose test analyses. This should not be capillary blood which yields inaccurate results (Dellinger et al. 2013). Tests typically take place every 2 to 4 hours, leaving patients vulnerable if glucose levels change without warning. Numerous glucose management protocols have been developed to achieve glycaemic control, some of which use computer-based algorithms. These protocols aim to maintain glucose levels in the healthy range, which is typically between 4.4 and 8.8 mmol/l, and base any change to the insulin infusion rate on either the absolute measured value or the change from the previous measurement.

Current practice includes devices which monitor glucose levels continuously and provide real-time trending data, so that clinicians can intervene if the patient's glucose value moves outside the target range. As with Space GlucoseControl, these devices allow the adoption of event-based protocols rather than time-based measurement protocols. However, the information provided by these continuous glucose monitors is intended to supplement, not replace, readings obtained from approved blood-glucose measuring devices, and should be confirmed before making any therapy adjustments.

NICE is not aware of other CE-marked devices that have a similar function to the Space GlucoseControl.

Costs and use of the technology

For intensive care units already using B. Braun infusion pumps, the cost for adding the Space GlucoseControl computer module is £5500 per unit. Where B. Braun infusion pumps are not already in use, the cost of equipping a bed space with the minimum configuration for the Space GlucoseControl system is £12,300.

B. Braun guarantees the components of the Space GlucoseControl system for 24 months, and the system is expected to have a lifespan of 10 years if it is used under normal cleaning and care circumstances. The manufacturer provides both the initial training and further training and education updates free of charge throughout the lifespan of the device. The system is subject to a technical safety check every 2 years, carried out by B. Braun-trained technicians. Individual service agreements take into account the specific requirements of each hospital. The eMPC computer module is an integral part of the system and cannot be used separately. No extra consumables are needed to use the

system.

Likely place in therapy

The Space GlucoseControl system is intended to be used where glycaemic control is particularly important, such as intensive care units. It is intended to replace manual dose calculation and administration of insulin, and ensure that insulin therapy responds to changes in nutrition.

Specialist commentator comments

One specialist commentator reported that the Space GlucoseControl system reaches the target blood-glucose range sooner and maintains it for longer than traditional protocols. They noted that for each patient there was an initial increase in workload while the sampling interval was high, followed by a reduction in workload once the target range was achieved. The commentator reported that some nurses were not confident that the 4-hour interval between samples suggested by the Space GlucoseControl was sufficient, and therefore took samples more frequently.

The commentator noted that the Space GlucoseControl system was suitable for all patient groups. However, patients having bolus doses of carbohydrate or corticosteroids cause the machine to increase the sampling frequency, increasing the operator workload. The commentator also reflected that sampling equipment should be consistent for each patient, because fluctuations between arterial and capillary blood affected the time taken to reach the target range.

Another commentator considered the evidence that glycaemic control improves clinical outcomes to be mixed, because tight glycaemic control protocols are associated with an increase in hypoglycaemic episodes. Although some degree of glycaemic control is thought to be beneficial, the best level is unclear, and the benefits may vary between patient groups. Using the Space GlucoseControl system may increase blood-glucose sampling above current levels, and it remains unclear whether there are significant patient benefits without additional resource use. Additionally, the specialist commentator noted that this system does not remove the risk of hypoglycaemia, and that evidence was needed to show that it could reduce this risk before its clinical or economic value could be assessed.

One commentator noted that although the manufacturer states that no consumables are needed for the Space GlucoseControl system, specific 'nutrition-giving sets' need to be used with the machine. Extra costs may therefore be incurred if the system were not being used for all patients in an intensive care unit; 2 different nutrition sets would need to be stocked. Moreover, if the unit is not already using B. Braun glucose pumps, and another glucose-infusion system is being used and interfaced with the Space GlucoseControl system, then B. Braun intravenous infusion sets would need to be purchased and stocked.

The commentator also reported that local protocols would be needed for using the Space GlucoseControl system, to specify when use of the system would start and for which patient groups it would be used, and also including a plan to manage hypoglycaemia. These protocols would form part of the training for use of the system, provide consistent management of glucose control, and clarify that the Space GlucoseControl system is not intended to replace clinical expertise.

Equality considerations

NICE is committed to promoting equality and eliminating unlawful discrimination. We aim to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women, and
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief, in the way we produce our guidance (these are protected characteristics under the Equality Act [2010]).

Men aged 70–74 and women aged 75–79 are treated in intensive care more often than people in any other age group. Age is a protected characteristic under the Equality Act (2010).

Evidence review

Clinical and technical evidence

Regulatory bodies

No reports of adverse events were identified from searches of the Medicines and Healthcare Products Regulatory Agency (MHRA) website, or from the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

A literature search identified 2 fully published prospective non-controlled cohort studies of the Space GlucoseControl system (summarised in tables 1–4). Additionally, 4 randomised controlled trials and 1 non-controlled cohort study of the enhanced model predictive control (eMPC) algorithm (summarised in tables 5–14) were identified. The eMPC algorithm is a key part of the integrated Space GlucoseControl system, and so studies of the eMPC were judged to be relevant to this briefing. Also included were published abstracts of 2 studies of the Space GlucoseControl system and 1 study of the eMPC algorithm (table 15). Four relevant registered studies were identified that were completed, but no related publications were identified (table 16).

Clinical evidence on the Space GlucoseControl system

In the non-controlled cohort study by Amrein et al. (2014, summarised in tables 1 and 2), the Space GlucoseControl system was used for glycaemic management in 40 critically ill adult patients whose blood glucose level was greater than 6.1 mmol/l or who were already on insulin therapy. The study was conducted in 2 intensive care units. The primary outcome was the percentage of time that patient blood-glucose was maintained within the target range of 4.4–8.3 mmol/l. The follow-up period was 6.5 (standard deviation [SD]±3.7) days.

The predefined target glucose range was reached for a mean 88.3% of the time (SD±9.3%) and the mean arterial blood glucose was 6.7 mmol/l (SD±0.4) during the study period. The mean sampling interval was 2.2 hours (SD±0.4). The mean percentage of time spent in a

moderately hypoglycaemic range was 0.07% (SD±0.26%). There was 1 severe hypoglycaemic episode (2.5% of patients or 0.03% of glucose readings). There was a high rate of adherence to the suggested insulin dose; out of 3285 occasions, the eMPC advice was over-ruled in 59 (1.8%) The mean daily insulin dose was 87.2 (SD ±64.6) insulin units.

In the non-controlled cohort study by Kulnik et al. (2008, summarised in tables 3 and 4), the Space GlucoseControl system was used in 10 intensive care patients who were mechanically ventilated and who either had a blood-glucose level of more than 6.1 mmol/l or who were already on insulin therapy. The follow-up period was 72 hours. The primary outcome was glucose control, which was assessed by the percentage of time in the predefined glucose target range of 4.4–6.1 mmol/l.

The mean percentage of time spent in the target blood-glucose range was 47.0% (SD±13.0%). The average blood-glucose concentration was 6.05 mmol/l (SD±0.72 mmol/l) and the average hyperglycaemic index was 0.55 mmol/l (SD±0.50 mmol/l). No hypoglycaemic episodes (blood glucose of less than 2.2 mmol/l) were detected. The nurses overruled the given advice of the system 11 times (1.5% of all given advice). Treatment had to be stopped ahead of schedule in 3 patients because of several technical malfunctions (failures of system integration).

Table 1 Summary of the Amrein et al. (2014) study

Study component	Description
Objectives/ hypotheses	To investigate the performance of the Space GlucoseControl system, which is a nurse-driven, computer-assisted device for glycaemic control combining infusion pumps with the enhanced Model Predictive Control algorithm, in medical critically ill patients in 2 ICU sites. The primary aim was to evaluate the complete strict glucose control system in these patients at the 2 different sites.
Study design	Prospective non-controlled open clinical investigation.
Setting	The study was conducted in 2 medical ICUs in tertiary centres in Graz, Austria and Zurich, Switzerland. Outcomes were reported for a period of 6.5 days (SD=3.7).

Inclusion/ exclusion criteria	Inclusion criteria: adult medical ICU patients, blood glucose >6.1 mmol/l or already on insulin therapy, presumed to stay ≥72 hours at the ICU. Exclusion criteria: insulin allergy, presence of ketoacidosis, moribund patients likely to die within 24 hours.
Primary outcomes	Glucose control assessed by the percentage of time within the predefined glucose the target range (4.4–8.3 mmol/l).
Statistical methods	Data analysis was performed using SPSS version 19.0, on an ITT basis. Intermediate blood glucose values were linearly interpolated.
Participants	Adult medical ICU patients with blood glucose >6.1 mmol/l or already on insulin therapy (n=40).
Results*	For the study period, the predefined target glucose range was reached in 88.3% (SD± 9.3%) of time and mean arterial blood glucose was 6.7 (SD ±0.4) mmol/l. The mean sampling interval was 2.2 (SD ±0.4) hours. The percentage of time spent in a moderately hypoglycaemic range (2.2–3.3 mmol/l) was 0.07% (SD ±0.26%). One severe hypoglycaemic episode (<2.2 mmol/l) occurred (2.5% of patients or 0.03% of glucose readings). There was a high adherence to the given insulin dose advice (98.2%) and the mean daily insulin dose was 87.2 (SD±64.6) IU. Six patients died during the study period.
Conclusions	The authors concluded that the Space GlucoseControl system is a safe and efficient method to control blood glucose in critically ill patients as assessed in 2 European medical ICUs.
Abbreviations: ICU, intensive care unit; IU, insulin unit; ITT, intention to treat; SD, standard deviation. *Data reported as mean (SD).	

Table 2 Summary of the Amrein et al. (2014) study outcomes

Outcome measures	**Results**[a]
Primary outcome (n=40)	
• Percentage of time within the predefined glucose the target range	88.3 (9.3)
Selected secondary outcomes (n=40)	

• Mean arterial blood glucose (mmol/l)	6.7 (0.4)
• Sampling interval (h)	2.2 (0.4)
• Mean daily insulin dose (IU)	87.2 (64.6)
• Adherence to the given insulin dose advice (%)	98.2
• Percentage of time spent in a moderately hypoglycaemic range[b]	0.07 (0.26)
Safety (n=40)	
• Patients reporting severe hypoglycaemic episodes; number (%)[c]	2.5% (1/40)
Abbreviations: h, hour; IU, insulin unit. [a] Data reported as mean (standard deviation) unless otherwise specified. [b] Moderately hypoglycaemic range was defined as 2.2–3.3 mmol/l. [c] Hypoglycaemia was defined as <2.2 mmol/l.	

Table 3 Summary of the Kulnik et al. (2008) study

Study component	Description
Objectives/ hypotheses	To test the performance (efficacy, safety, and usability) of the Space GlucoseControl system for tight glycaemic control in patients at a medical ICU for a period of 72 hours.
Study design	Prospective non-controlled open clinical investigation.
Setting	The study was conducted at a medical ICU in Medical University of Graz. Follow-up duration was 72 hours.

Inclusion/ exclusion criteria	Inclusion criteria: adult medical ICU patients; mechanically ventilated and presumed to need at least 3 days of intensive care; blood glucose level >6.1 mmol/l or already on insulin therapy.
Primary outcomes	Blood glucose control assessed by percentage of time in the predefined glucose target range 4.4-6.1 mmol/l (arterial blood glucose measurements).
Statistical methods	Statistical analysis was performed on an ITT basis. Data were reported as mean (SD) if not otherwise indicated. Normality of data was checked by Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparison of glucose data with results from historical data, Kruskall-Wallis and subsequent Mann-Whitney U tests with Bonferroni correction for group comparisons were applied. Data analysis was performed using SPSS version 15.0.
Participants	Mechanically ventilated adult medical ICU patients with blood glucose >6.1 mmol/l or already on insulin therapy (n=10).
Results[a]	The percentage of values in time in target was 47.0% (SD±13.0%). The average blood glucose concentration and hyperglycaemic index were 6.05 mmol/l (SD±0.72) and 0.55 mmol/l (SD ±0.50) respectively. No hypoglycaemic episode (<2.2 mmol/l) was detected. The nurses overruled the given advice of the system 11 times (1.5% of all given advice). The treatment had to be stopped ahead of schedule in 3 patients due to several technical malfunctions of the device (failures of system integration, such as repetitive error messages and missing data in the data log due to communication problems between the new hardware components are shortcomings of the present version of the device).
Conclusions	The authors concluded that tight glycaemic control in patients at a medical ICU could be established following the advice of the decision support system. Accordingly, and with technical improvement required, the system had the capacity to be a reliable tool for routine establishment of glycaemic control for critically ill patients.

Abbreviations: ICU, intensive care unit; ITT, intention to treat.

[a] Data reported as mean (standard deviation).

Table 4 Summary of the Kulnik et al. (2008) study outcomes

Outcome measures	Results[a]
Primary outcome (n=10)	
• Percentage of time within the predefined glucose the target range (%)	47.0 (13.0)
Selected secondary outcomes (n=40)	
• Mean arterial blood glucose (mmol/l)	6.05 (0.72)
• Hyperglycaemic index (mmol/l)	0.55 (0.50)
• Percentage of values below 3.3 mmol/l (%)	0.53 (0.88)
• Percentage of values above 8.3 mmol/l (%)	6.65 (8.79)
• Insulin rate (IU/h)	4.2 (2.8)
• Total carbohydrate administration (g/h)	7.5 (2.0)
• Sampling interval (minute)[b]	86.3 (26.0)
• Occasions of the nurses overruling the given advice of the system	11 (1.5%)
Safety (n=10)	
• Patients reporting hypoglycaemia episode[c]	0

Abbreviations: h, hour, IU, insulin unit.

[a] Data reported as mean (standard deviation) unless otherwise specified.

[b] Defined as input of glucose values into the system.

[c] Hypoglycaemia was defined as <2.2 mmol/l.

Clinical evidence on the eMPC algorithm

In the studies of the eMPC algorithm, the program was installed on bedside computers. All other routine patient care, including nutritional administration, was done according to existing protocols.

In the Hovorka et al. (2007) trial (summarised in tables 5 and 6), 60 critically ill adults admitted for major elective cardiac surgery were randomly assigned to either the eMPC algorithm with a variable sampling rate (n=30), or a routine glucose management protocol (n=30). The treatment visit was at the start of surgery and continued for up to 24 hours at the ICU. The main outcome measures were mean blood glucose, percentage of time in the target range, and the number of severe hypoglycaemia events.

Compared with routine management, the eMPC algorithm achieved significantly better blood-glucose control with a mean blood-glucose level of 6.2 mmol/l (SD±11.1) compared with 7.2 mmol/l (SD±1.1, $p<0.05$), and mean percentage of time in the target range of 60.4% (SD±22.8%) compared with 27.5% (SD±16.2%, $p<0.05$). There was no severe hypoglycaemia in either of the groups. In the eMPC group there was a significantly higher insulin infusion rate (4.7 IU/h [SD±3.3] compared with 2.6 IU/h [SD±1.7], $p<0.05$) and shorter mean sampling interval (1.5 hours [SD±0.3] compared with 2.1 hours (SD±0.2), $p<0.05$).

In the Pachler et al. (2008) trial (summarised in tables 7 and 8), 50 intensive care patients who were mechanically ventilated and who had a blood glucose level of more than 6.1 mmol/l, or who were already on insulin therapy, were randomly assigned to care using either the eMPC algorithm or the standard insulin treatment algorithm. Outcomes were measured at days 1, 2 and 3. The primary outcome was blood-glucose control measured as hyperglycaemic index, which was defined as the area under the curve above the upper limit of normal (glucose level 6.1 mmol/l, modified from the original 6.0 mmol/l) divided by the total length of stay (time in study).

The eMPC group had significantly lower hyperglycaemic index (0.4 mmol/l [0.2–0.9] compared with 1.6 mmol/l [1.1–2.4], $p<0.001$) and blood glucose (5.9 mmol/l [5.5–6.3] compared with 7.4 mmol/l [6.9–8.6], $p<0.001$) than the standard care group (both measured as median (inter-quartile range). One patient in the eMPC group had a hypoglycaemic episode compared with no patients in the standard care group. Mean sampling interval was significantly shorter in the eMPC group (117 minutes [SD±34] compared with 174 minutes [SD±27], $p<0.001$).

The Blaha et al. (2009) trial (summarised in tables 9 and 10) compared 3 insulin-titration protocols for tight glycaemic control: the eMPC algorithm; the Matias protocol (based on absolute glucose value) and the Bath protocol (based on relative glucose change). A total of 120 adults who were admitted to a postoperative intensive care unit after elective cardiac surgery were randomised to 1 of the 3 protocols. Follow-up data were recorded for up to 48 hours and used for the comparison.

The eMPC protocol group had statistically significantly lower blood glucose than either the Matias or the Bath group. This was evident from data compared over the entire study period, or data at 48 hours after reaching the target blood-glucose range.

For patients in the eMPC group, the time taken to reach the target blood-glucose range was statistically significantly shorter than with the Bath protocol, but was not significantly different from that of the Matias protocol. Patients in the eMPC group also were also in the target blood-glucose range for statistically significantly more time than those in the other groups. There was no significant difference between the protocols in terms of severe hypoglycaemia episodes or percentage of time in hypoglycaemia. Compared with those in either the Matias or the Bath group, patients in the eMPC group had a significantly higher percentage of time at risk of hypoglycaemia, and a significantly lower percentage of time in or at risk of hyperglycaemia.

There was no significant difference in sampling interval between the 3 protocols over the entire study period. After reaching the target range, the sampling interval was statistically significantly longer in the eMPC group than in the Bath protocol group, but there was no significant difference between the eMPC and Matias groups.

The Cordingley et al. (2009) trial (summarised in tables 11 and 12) studied the effectiveness of the eMPC algorithm compared with individual standard insulin management regimens in critically ill patients in 2 intensive care units: Royal Brompton Hospital London and University Hospital Gasthuisberg Leuven. A total of 34 patients were recruited. In each ICU, patients were randomised to care with either the eMPC algorithm or the intensive care unit's standard insulin infusion management regimen. The study duration was 72 hours. A number of outcome measures were compared by management protocol, as well as between the eMPC and standard care by intensive care unit, including: blood-glucose control, insulin infusion rates and alterations to the insulin infusion rate, and carbohydrate administration rates and number of alterations in administration rate.

In comparing the eMPC and standard care, the 2 units showed contradictory results for

blood-glucose concentration, hyperglycaemic index, time taken to achieve glucose control, percentage of time in target glucose range, and insulin infusion rates or alteration to insulin infusion rate. For example, in the London unit, the eMPC achieved statistically significantly better blood-glucose control than standard care, but the opposite was true in the Leuven unit (table 12).

The non-controlled study by Amrein et al. (2010, summarised in tables 13 and 14) investigated the use of the eMPC algorithm in 20 critically ill patients for the length of their stay in intensive care. The primary outcome measure was blood-glucose control measured by percentage of time in target blood-glucose range. Percentage of time in target range was 58.12% (SD±10.05%). Three hypoglycaemic episodes occurred in 3 patients, corresponding to a rate of 0.02 episodes per treatment day. Mean blood-glucose concentration was 5.8 mmol/l (SD±0.5), and mean insulin need was 101.3 IU/day (SD±50.7). Mean carbohydrate intake (enteral and parenteral nutrition) was 176.4 g/day (SD±61.9).

Table 5 Summary of the Hovorka et al. (2007) trial

Study component	Description
Objectives/ hypotheses	To compare blood glucose control with the eMPC computer-based model predictive control algorithm with a variable sampling rate, against a routine glucose management protocol during the peri- and post-operative periods of elective cardiac surgery.
Study design	Single-centre non-blinded randomised controlled trial.
Setting	The study was performed at the Department of Cardiac Surgery, General University Hospital, Prague. A screening visit was performed 1 day before the surgery. The treatment visit was the start of surgery and continued for up to 24 hours at the ICU.
Inclusion/ exclusion criteria	Inclusion criteria were not specified, but it was stated that threshold glucose level was not defined as an inclusion criterion. Exclusion criteria: insulin allergy, mental incapacity, and language barrier.
Primary outcomes	The main outcome measures were mean blood glucose, percentage of time in target range (4.4-6.1 mmol/l), and hypoglycaemia events.

Statistical methods	The analysis was performed using SigmaStat (Jandel Scientific). The results are expressed as mean (SD). Differences between the comparison groups were evaluated using the t-test or Mann-Whitney U rank sum test as appropriate. No sample size calculation was stated.
Participants	Participants were adult patients admitted for major elective cardiac surgery (n=60).
Results	Blood glucose control was better with the eMPC than the routine management for mean blood glucose and percentage of time in the target range. No severe hypoglycaemia occurred in either of the groups. Under the eMPC there was a higher insulin infusion rate and shorter mean sampling interval.
Conclusions	The authors concluded that, compared with routine glucose management protocol, the eMPC algorithm was more effective and comparably safe in maintaining euglycemia in cardiac surgery patients.
Abbreviations: eMPC, enhanced model predictive control; ICU, intensive care unit; n, number of patients; SD, standard deviation.	

Table 6 Summary of the Hovorka et al. (2007) trial outcomes[a]

	eMPC	Routine protocol	Analysis
Randomised	n=30	n=30	
Efficacy	n=30	n=30	
Primary outcomes			
• Blood glucose at operating theatre (mmol/l)	6.6 (1.8)	7.1 (1.2)	p<0.01
• Blood glucose at ICU (mmol/l)	6.0 (1.0)	7.3 (1.3)	p<0.01
• Percentage of time in target range (%)	27.5 (16.2)	60.4 (22.8)	p<0.01
• Number of severe hypoglycaemia (<2.9 mmol/l)	0	0	

Selected secondary outcomes			
• Time in target range (h)	14.5 (5.5)	6.6 (3.9)	p<0.01
• Number of severe hypoglycaemia (blood glucose <2.9 mmol/l) event	0	0	N/A
• Average insulin rate (IU/h)	4.7 (3.3)	2.6 (1.7)	p<0.01
• Time above target range (h)	7.4 (4.7)	16.7 (4.1)	p<0.01
• Total insulin dose (IU/24 hour)	111 (67)	69 (45)	p<0.01
• Time under target range (h)	1.9 (1.7)	0.6 (1.5)	p<0.01
• Average sampling interval (h)	1.5 (0.3)	2.1 (0.2)	p<0.01
Abbreviations: eMPC, enhanced model predictive control; h, hour; ICU, intensive care unit; N/A, not applicable; n, number of patients; p, p value; SD, standard deviation. [a] Outcomes were measured as mean (standard deviation) unless otherwise specified.			

Table 7 Summary of the Pachler et al. (2008) trial

Study component	Description
Objectives/ hypotheses	To demonstrate that glycaemic control as established by the eMPC algorithm is not inferior to that achieved by the standard insulin treatment algorithm implemented in a medical ICU.
Study design	Single-centre non-blinded randomised controlled trial. Randomisation was performed using serial numbers with concealment.
Setting	The study was conducted in a medical ICU in a tertiary teaching hospital, Graz. Follow-up period was 72 hours and the outcomes were measured at day 1, day 2 and day 3.

Inclusion/ exclusion criteria	Inclusion criteria: mechanically ventilated adult medical ICU patients, presumed to require at least 3 days of intensive care, and blood glucose >6.1 mmol/l or already on insulin therapy. No exclusion criteria were specified.
Primary outcomes	Glucose control, measured as hyperglycaemic index defined as the area under the curve above the upper limit of normal (glucose level 6.1 mmol/l, modified from the original 6.0 mmol/l) divided by the total length of stay (time in study).
Statistical methods	Sample size was calculated based on non-inferiority analysis; a significance level of 0.025 and a power of 80% were defined. Data were tested for normality and subsequently comparisons between groups were performed using unpaired student t test or the Mann-Whitney U-test as necessary. The conventional significance level of alpha=0.05 was used. The SPSS13.0.1 software package was applied for the statistical analysis, which was performed on an ITT basis.
Participants	Mechanically ventilated medical ICU patients (n=50) with glucose >6.1 mmol/l or already on insulin therapy.
Results	Compared with the control group, the eMPC group had significantly lower hyperglycaemic index and blood glucose. There was one hypoglycaemic episode in the eMPC with none in the control group. Sampling interval was significantly shorter in the eMPC group than in the control.
Conclusions	The authors concluded that, the eMPC algorithm was effective in maintaining tight glycaemic control in severely ill medical ICU patients.
Abbreviations: eMPC, enhanced model predictive control; ITT, intention to treat; ICU, intensive care unit; n, number of patients.	

Table 8 Summary of the Pachler et al. (2008) trial outcomes

	eMPC	Standard care	Analysis
Randomised	n=25	n=25	
Efficacy	n=25	n=25	

Primary outcome			
• Hyperglycaemic index (mmol/l), median (IQR)	0.4 (0.2–0.9)	1.6 (1.1–2.4)	p<0.001
– Day 1	0.5 (0.1–1.0)	1.6 (0.7–2.9)	p<0.01
– Day 2	0.4 (0.1–1.0)	1.6 (1.1–2.7)	p<0.001
– Day 3	0.1 (0.0–0.3)	1.0 (0.5–2.0)	p<0.001
Selected secondary outcomes			
• Blood glucose (mmol/l), median (IQR)	5.9 (5.5–6.3)	7.4 (6.9–8.6)	p<0.001
– Day 1	5.9 (5.5–7.0)	7.8 (6.5–9.5)	p<0.001
– Day 2	6.1 (5.4–6.9)	7.6 (7.2–8.8)	p<0.001
– Day 3	5.3 (5.1–5.7)	7.1 (6.2–8.1)	p<0.001
• Sampling interval (min), mean (SD)	117 (34)	174 (27)	p<0.001
– Day 1	110 (30)	162 (34)	p<0.001
– Day 2	127 (46)	196 (43)	p<0.001
– Day 3	134 (44)	187 (31)	p<0.001
• Insulin administration (IU/h), median (IQR)	3.0 (2.0–5.6)	2.3 (1.7–4.0)	p=0.22
– Day 1	3.4 (1.4–6.0)	2.7 (1.4–3.6)	NS
– Day 2	3.2 (1.8–6.6)	2.1 (1.6–4.7)	NS

– Day 3	3.5 (2.4–7.2)	2.2 (1.4–4.8)	NS
• Insulin rate alteration during the 72 h (occasions), mean (SD)	35.5 (12.7)	12.0 (4.2)	p<0.001
• Total carbohydrate administration (g/h), mean (SD)	7.1 (3.4)	7.1 (2.5)	p=0.97
– Day 1	5.5 (3.4)	5.7 (3.4)	NS
– Day 2	8.3 (3.8)	7.8 (3.1)	NS
– Day 3	8.8 (2.9)	7.8 (3.0)	NS
Abbreviations: eMPC, enhanced model predictive control; h, hour; IQR, inter quartile range; NS, no statistical significance; n, number of patients; p, p value; SD, standard deviation.			

Table 9 Summary of the Blaha et al. (2009) trial

Study component	Description
Objectives/ hypotheses	To compare 3 insulin-titration protocols for tight glycaemic control in a surgical intensive care unit in patients admitted to the postoperative ICU after elective cardiac surgery: the enhanced model predictive control (eMPC) algorithm, a computer-based model predictive control algorithm with variable sampling rate; the Matias protocol which was based on the absolute glucose value; the Bath protocol, based on the relative glucose change.
Study design	A single-centre open-label randomised trial.
Setting	A surgical ICU at a university hospital, Prague. Only data for up to 48 hours were used for the comparison of the 3 protocols.
Inclusion/ exclusion criteria	Patients included were aged 18–90 years and admitted to the postoperative ICU after elective cardiac surgery. Exclusion criteria were insulin allergy, mental incapacity, and language barrier.

Primary outcomes	Not specified. Outcomes measured: • entire study average glycaemia level • time to the target range (4.4–6.1 mmol/l) • average glucose level after the target range was reached • number of hypoglycaemic episodes (blood glucose <2.9 mmol/l) • time within the target range • time between 2.9 and 4.3 mmol/l with no clinical manifestations of hypoglycaemia but indicating risk for hypoglycaemia • time between 6.2 and 8.3 mmol/l indicating risk of hyperglycaemia • time in >8.3 mmol/l indicating hyperglycaemia • sampling interval, which indicates workload.
Statistical methods	Data analysis was performed using STATISTICA software. The three insulin-titration protocols were compared using ANOVA followed by a Holm-Sidak test, Student's t-test, or Mann-Whitney U test as appropriate. The significance level was set at p=0.05. No sample size calculation was stated.
Participants	Patients aged 18 to 90 years and admitted to the postoperative ICU after elective cardiac surgery (n=120).

Results	For both the entire study period of 48 hours and after reaching the target range, the eMPC protocol group had significantly lower blood glucose than either the Matias or the Bath group. For the eMPC, the time to target range was significantly shorter compared with the Bath, but was not significantly different from that of the Matias. The eMPC had significantly longer time within the target range and significantly higher percentage of time within the target range compared with either the Matias or the Bath. There was no significant difference between the protocols for severe hypoglycaemia episodes or percentage of time in hypoglycaemia. Compared with either the Matias or the Bath group, the eMPC group had significantly higher percentage of time in risk of hypoglycaemia, and significantly lower percentage of time in hyperglycaemia and percentage of time in risk of hyperglycaemia. There was no significantly difference in sampling interval for the entire study period between the 3 protocols. After reaching the target range, sampling interval was significantly longer in the eMPC group than in the Bath with no significant difference between the eMPC and the Matias groups.
Conclusions	The authors concluded that the eMPC algorithm provided the best tight glycaemic control without increasing the risk of severe hypoglycaemia, while needing the fewest glucose measurements compared with the Matias and Bath protocols. Overall, all 3-protocols were safe and effective in the maintenance of tight glycaemic control in cardiac surgery patients.
Abbreviations: ANOVA, analysis of variance; eMPC, enhanced model predictive control; ICU, intensive care unit; n, number of patients; p, p value.	

Table 10 Summary of the Blaha et al. (2009) trial outcomes

	eMPC	Matias	Bath	Analysis
Randomised	n=40	n=40	n=40	
Efficacy	n=40	n=40	n=40	
Outcomes (not specified which was primary outcome)[a]				

Entire study blood glucose control data (or 48 h)				
• Average blood glucose (mmol/l)	5.9 (0.2)	6.7 (0.1)	6.5 (0.2)	p<0.05 for eMPC vs either Matias or Bath
• Sampling interval (h)	2.1 (0.1)	2.0 (0.1)	1.7 (0.1)	NS
• Time to target range (h)	8.8 (2.2)	10.9 (1.0)	12.3 (1.9)	p<0.05 for eMPC vs Bath; NS for eMPC vs Matias
• Percentage of time in target range (%)	46.0 (3.0)	38.2 (2.9)	39.7 (3.1)	p<0.05 for eMPC vs either Matias or Bath
Blood glucose control after reaching the target range				
• Average blood glucose (mmol/l)	5.2 (0.1)	6.2 (0.1)	5.8 (0.1)	p<0.05 for eMPC vs either Matias or Bath
• Sampling interval (h)	2.3 (0.1)	2.1 (0.1)	1.8 (0.1)	p<0.05 for eMPC vs Bath; NS for eMPC vs Matias
• Time in target range (h)	62.8 (4.4)	48.4 (3.2)	55.5 (3.2)	p<0.05 for eMPC vs either Matias or Bath
• Percentage of time in risk of hypoglycaemia (%)	22.2 (1.9)	10.9 (1.5)	13.1 (1.6)	p<0.05 for eMPC vs either Matias or Bath
• Percentage of time in hypoglycaemia (%)	0.0 (0.0)	0.4 (0.2)	0.4 (0.3)	NS
• Severe hypoglycaemia episodes	0	1	2	NS

• Percentage of time in risk of hyperglycaemia (%)	13.7 (2.6)	27.5 (2.2)	24.5 (2.4)	p<0.05 for eMPC vs either Matias or Bath
• Percentage of time in hyperglycaemia (%)	1.3 (1.2)	12.8 (2.2)	6.5 (2.0)	p<0.05 for eMPC vs either Matias or Bath
Abbreviations: eMPC, enhanced model predictive control; h, hour; NS, no statistical significance; n, number of patients; p, p value; SEM, standard error of the mean; vs, versus. [a] Data reported as mean (SEM).				

Table 11 Summary of the Cordingley et al. (2009) trial

Study component	Description
Objectives/ hypotheses	To investigate the effectiveness of the eMPC algorithm for intravenous insulin infusion aimed at achieving tight glucose control in critically ill patients in 2 intensive care units (RBH and KUL) compared with standard insulin management regimens.
Study design	Randomised, controlled, open-label, 2-centre, feasibility study. Within each ICU, patients were randomised to intravenous insulin infusion advised by the eMPC algorithm or the respective ICU's standard insulin infusion management regimen.
Setting	Two adult ICUs in University Hospitals (in London and Leuven); study duration was 72 hours.
Inclusion/ exclusion criteria	Patients admitted to ICU, aged at least 18 years, with arterial plasma glucose greater than 120 mg/dl (6.7 mmol/l) or already receiving intravenous insulin infusion, and expected to be receiving mechanical ventilation for more than 72 hours from the study start. Patients with known diabetes mellitus were not excluded. Exclusion criteria: known allergy to insulin and chronic mental incapacity.

Primary outcomes	The following outcome measures were compared between the ICUs by management protocol, as well as between eMPC and standard care by ICU: • glucose control, measured by — arterial glucose concentration (mean blood glucose and time weighted mean glucose concentrations) — time for plasma glucose levels to reach the target (4.4-6.1 mmol/l) — hyperglycaemic index (calculated as the area of the glucose-time concentration curve above 6.1 mmol/l divided by the time of the study) — glucose measurement interval. • mean insulin infusion rates and alterations to the insulin infusion rate; • carbohydrate administration rates and number of alterations in administration rate.
Statistical methods	Student t-test or Mann-Whitney U test was used when appropriate for continuous data and Fisher's exact test for categorical data (GraphPad Prism). A p value of <0.05 was taken to signify statistical significance. No sample size calculation was stated.
Participants	Participants were critically ill patients (n=34) with hyperglycaemia (glucose>120 mg/dl;6.7 mmol/l) or already receiving insulin infusion.
Results	The comparison of eMPC and the standard care showed differences that were contrary for each ICU for blood glucose concentration, hyperglycaemic index, time to achieve glucose control, percentage of time in target glucose range, and insulin infusion rates or alteration to insulin infusion rate. For example, in the RBH ICU the eMPC achieved significantly better blood glucose control than the standard care, while in the KUL ICU the standard care achieved significantly better blood glucose control.

Conclusions	The authors concluded that the eMPC algorithm provided similar, effective and safe tight glucose control over 72 hours in critically ill patients in 2 different ICUs. Further development is required to reduce glucose sampling interval while maintaining a low risk of hypoglycaemia.
Abbreviations: eMPC, enhanced Model Predictive Control; ICU, intensive care unit; KUL, University Hospital Gasthuisberg, Leuven; n, number of patients; RBH, Royal Brompton Hospital, London.	

Table 12 Summary of the Cordingley et al. (2009) trial outcomes

	eMPC	Standard care	Analysis
Randomised	n=16	n=18	
Efficacy	n=16	n=18	
Outcomes[a]			
• Blood glucose for the 72 hours (mmol/l), mean (SD)			
– RBH	6.0 (0.28)	7.1 (0.50)	p<0.001
– KUL	6.2 (0.22)	5.7 (0.28)	p<0.01
• Time-weighted blood glucose for the 72 hours (mmol/l)			
– RBH	5.9 (0.28)	7.1 (0.50)	p<0.001
– KUL	5.7 (0.22)	97 (0.28)	p<0.05
• Hyperglycaemic index (above 6.1 mmol/l)			
– RBH	0.50 (0.30)	1.20 (0.50)	p<0.0001
– KUL	0.31 (0.16)	0.27 (0.14)	NS
• Time to achieve glucose control (minutes), mean (SD)			
– RBH	257 (96)	473 (431)	p<0.0001
– KUL	465 (180)	359 (236)	NS

• Percentage of time in target glucose range (%), median (range)			
– RBH	57.7 (46.5–72.3)	23.5 (12.9–66.3)	p<0.01
– KUL	66.1 (52.3–85.9)	63.4 (38.1–80.5)	p>0.05
• Glucose measurement interval (hours), mean (SD)			
– RBH	1.1 (0.06)	1.9 (0.7)	P=0.02
– KUL	1.8 (0.4)	2.5 (0.4)	p<0.01
• Insulin infusion rates (U/h), mean (SD)			
– RBH	4.1 (2.7)	3.1 (1.8)	P=0.5
– KUL	5.2 (2.6)	4.1 (2.5)	NS
• Alteration to insulin infusion rates (occasions/h), median (range)			
– RBH	Not reported	Not reported	NS
– KUL	14 (10–23)	5.4 (3–9)	p<0.0001
• Parenteral CHO administration (g/h), mean (SD)			
– RBH	Not reported	Not reported	NS
– KUL	10.6 (3.1)	10.5 (3.8)	NS
• Enteral feeding CHO administration (g/hour), mean (SD)			
– RBH	Not reported	Not reported	NS
– KUL	0.5 (1.0)	1.4 (4.2)	NS

Abbreviations: CHO, carbohydrate; CI, confidence interval; h, hour; KUL: University Hospital Gasthuisberg, Leuven; NS, no statistical significance; n, number of patients; p, p value; RBH, Royal Brompton Hospital, London; SD: standard deviation.

[a] There are some minor discrepancies on the result figures between table 3, 4 and 5 and the text in the study paper.

Table 13 Summary of the Amrein et al. (2010) study

Study component	Description
Objectives/ hypotheses	To investigate the of the eMPC algorithm for glycaemic control in medical critically ill patients for the whole length of intensive care unit stay.
Study design	Prospective non-controlled open clinical investigation.
Setting	The study was conducted at a medical ICU in Medical University of Graz from Sep 2008 to Jan 2009. Follow-up duration was the whole length of intensive care unit stay.
Inclusion/ exclusion criteria	Inclusion criteria: adult medical ICU patients; assumed to require at least 5 days of intensive care treatment; blood glucose level>6.1 mmol/l or already on insulin therapy. Exclusion criteria: insulin allergy; presence of ketoacidosis.
Primary outcomes	Blood glucose control assessed by: percentage of time within the predefined glucose target range (4.4–6.1 mmol/l, arterial blood glucose measurements).
Statistical methods	Statistical analysis was performed on an ITT basis. Data were reported as mean (SD) if not otherwise indicated. For the day-by-day comparison of blood glucose values, the Friedeman test and the nonparametric test were used. Data analysis was performed using SPSS version 14.0.
Participants	Adult medical ICU patients with blood glucose >6.1mmol/l or already on insulin therapy (n=20).

Results[a]	During the study period of 7.3 days (median; interquartile range 4.4–10.2), the percentage of values in time in target was 58.12 % (10.05). For all patients with at least 7 days in the ICU, there was no statistically significant difference between the daily mean percentage of times in target range in respect of the averages. Mean blood glucose concentration was 5.8 (0.5) mmol/l. Insulin requirement was 101.3 (50.7) IU. Mean carbohydrate intake (enteral and parenteral nutrition) was 176.4 (61.9) g/day. Three hypoglycaemic episodes occurred in three subjects, corresponding to a rate of 0.02 per treatment day.
Conclusions	The authors concluded that, in the study the eMPC algorithm was a safe and reliable method to control blood glucose in critically medical ICU patients for the whole length of ICU stay.
Abbreviations: ICU, intensive care unit; ITT, intention to treat; mmol/l, millimoles per litre; n, number of patients. [a] Data reported as mean (standard deviation).	

Table 14 Summary of the Amrein et al. (2010) study outcomes

Outcome measures	**Results** [a]
Primary outcome (n=20)	
• Percentage of time within the predefined glucose (%)	58.12 (10.05)
Selected secondary outcomes (n=20)	
• Percentage of time with glucose<2.2 mmol/l predefined glucose (%)	0.02 (0.08)
• Percentage of time with glucose>8.3 mmol/l predefined glucose (%)	6.59 (7.15)
• Mean arterial blood glucose (mmol/l)	5.8 (0.5)
• Insulin rate (IU/day)	101.3 (50.7)

• Insulin rate (IU/h)	4.22
• Total carbohydrate administration (g/day)	176.4 (61.9)
• Sampling interval (h)	1.69
Safety (n=20)	
• Patients with severe hypoglycaemia episode (n) [b]	3
Abbreviations: h, hour; mmol/l, millimoles per litre; n, number of patients. [a] Data reported as mean (standard deviation) unless otherwise specified. [b] Severe hypoglycaemia was defined as <2.2 mmol/l.	

Clinical evidence on the Space GlucoseControl system or the eMPC algorithm presented as abstracts

Also included were published abstracts of 2 studies of the Space GlucoseControl system and 1 study of the eMPC algorithm (table 15).

Table 15 Abstracts of relevant studies

Study	Objective	Study design and follow-up	Population Comparison Outcome measures

Goss 2012	To compare glycaemic control using the B. Braun Space GlucoseControl system with standard Bath protocol.	Retrospective cohort study; data was compared from patients on Space GlucoseControl system from June 2011 to February 2012 with that from patients from March to December 2011 who had received the standard protocol.	Population: critically ill patients in the general ICU at the Royal Cornwall Hospital, Truro, UK. Comparison: • B. Braun Space GlucoseControl system (n=14) • standard Bath protocol (n=79). Outcome measure: • time spent in range (of 3.5-10.0 mmol/l) • hours out of range • mean blood glucose level • hypoglycaemic events.

Blaha 2014	To evaluate the performance (efficiency) of Space GlucoseControl system under routine conditions in adult ICU patients requiring blood glucose control.	The study had 7 centres from nine European countries and included a total of 508 patients. No further information in the abstract on study design and follow-up.	Population: adult ICU patients requiring blood glucose control (n=508). Comparison: • the B. Braun Space GlucoseControl system Outcome measure: The primary endpoint was the percentage of time within the target range, and secondary outcome measures were the frequency of hypoglycaemic episodes and blood glucose measurement intervals.

Roubicek 2007[a]	To compare blood glucose control by the eMPC algorithm (with variable sampling rate) with routine glucose management protocol in peri- and post-operative period in cardiac surgery patients.	Randomised controlled trial; follow-up 24 hours.	Population: patients in peri- and post-operative cardiac surgery period (n=20). Comparison: • eMPC (n=10) • routine management (n=10). Outcome measures: • mean blood glucose • percentage of time in target range (4.4–6.1 mmol/l) • percentage of time above the target range • average insulin infusion rate • severe hypoglycaemia episode.
Abbreviations: eMPC, enhanced model predictive control; ICU, intensive care unit; n, number of patients. [a] Article in Czech; not retrieved.			

Recent and ongoing studies

Four relevant registered studies were identified that were completed but no related publications were identified. Of the 4 relevant studies, 3 used the Space GlucoseControl system and the other used the eMPC algorithm alone (table 16).

Table 16 Summary of registered trials

ID	Status	Study design	PICO	Publication
NCT01886365	Completed	Randomised, open label	P: cardio-surgical patients undergoing cardiopulmonary bypass with blood cardioplegia, n=75. I: Space GlucoseControl. C: conventional therapy with a fixed insulin dosing scheme. O: time within a blood glucose corridor of 4.4–8.3 mmol/l (time frame: from start of cardiopulmonary bypass during surgery until discharge from ICU, which is approximately after 48–72 hrs).	Not identified

NCT01146847	Completed	Non-randomised, open label	P: surgical ICU patients, n=20. I: Space GlucoseControl system. C: N/A. O: arterial blood glucose values, percentage of time within predefined glucose target range 4.4–6.1 mmol/l (time frame: all blood glucose measurements from start of treatment until last glucose measurement under treatment, i.e. stop of intravenous insulin treatment, up to a maximum of 72 hours).	Not identified

NCT01233271	Completed	Non-randomised, open label	P: postoperative cardiac surgery patients in the ICU, n=10. I: Space GlucoseControl System (with incorporated software-algorithm eMPC). C: N/A. O: arterial blood glucose values, percentage of time within predefined glucose target range 4.4–8.3 mmol/l (time frame: all blood glucose measurements from start of treatment until last glucose measurement under treatment, i.e. stop of intravenous insulin treatment, up to a maximum of 48 hours).	*Listed on the register page*: Cordingley JJ, Vlasselaers D, Dormand NC, et al. Intensive insulin therapy: enhanced Model Predictive Control algorithm versus standard care. Intensive Care Med 2009; 35(1):123–8. Note: this publication does not appear to be a report of the patient group enrolled in the NCT01233271 registered trial. For example, in the Cordingley study the patients were admitted to ICU for various reasons (e.g. respiratory failure, major trauma), but in the registered trial patients were postoperative cardiac surgery patients in the ICU.

NCT00444171	Completed	Randomised, open label	P: cardiac surgery patients. I: eMPC . C: insulin infusion rate guided by in-house glucose management protocol. O: mean blood glucose; percentage of time in target range.	*Not identified*
Abbreviations: C, comparator; I, intervention; ICU, intensive care unit; n, number of patients; N/A, not applicable; O, outcome; P, population.				

Costs and resource consequences

It is not clear what effect the use of this system would have on staffing costs in intensive care units. Intensive care involves frequent and sometimes continuous monitoring of many parameters, including not only glucose levels but also heart rate, blood pressure, temperature, oxygen saturation and electrolyte balance. It is not known what proportion of nurse time is needed specifically for glucose monitoring and insulin adjustment. So, although using the Space GlucoseControl system may save nurse-time, that saving may not be realised and cannot be presumed to lead to lower nurse costs.

Clinical studies have shown that tight control of blood-glucose levels in critically ill patients can lead to significant improvements in mortality and morbidity. If the Space GlucoseControl system leads to improved blood-glucose control compared with current protocols, there would be financial benefits from reduction in time spent in intensive care, and the associated health risks. At present, there is no published information on the extent of any such benefits, and hence any cost and resource consequences.

Capital costs of adopting the system depend on each site's current arrangements. For intensive care units already using the B. Braun pump system, the computer module may be purchased as an add-on. Intensive care units using manual monitoring and insulin administration would need to purchase the complete system, as would those units

currently using other types of automated monitoring and pump systems. The manufacturer claims that there is no effect on the consumables. No published evidence on resource consequences was identified.

Strengths and limitations of the evidence

Two published studies of the Space GlucoseControl system were identified. Both were non-controlled and designed to investigate the performance of the system, rather than to compare it with any other management system. The studies were small, with a total of 50 people enrolled in both the Amrein et al. (2014) and Kulnik et al. (2008) studies.

Four randomised controlled trials and 1 non-controlled cohort study of the eMPC algorithm were identified. None explicitly stated whether the eMPC algorithm was used as part of using B. Braun infusion pumps and the Space GlucoseControl system, and therefore these data must be treated with some caution.

The 4 trials were all small, with sample sizes ranging from 34 to 120 patients and 16 to 40 people in the treatment arms of each trial. Only 1 study (Pachler et al. 2007) had a sample size calculation, and this was based on non-inferiority analysis. The same study was the only 1 which specified randomisation methods and concealment (the randomisation was conducted using serially numbered, sealed envelopes). In the Cordingley et al. (2009) study, patients were randomised in each of the 2 intensive care units; furthermore, each intensive care unit had its own standard management regimen as the control. The comparability between the eMPC algorithm and the control regimen for all trial patients was therefore questionable. None of the studies was blinded, so investigators knew which treatment patients had, and this could be a source of bias. The non-controlled cohort study of the eMPC algorithm (Amrein et al. 2010) was designed to investigate the performance of the algorithm rather than to compare it with any other management system. This study was also small, including only 20 patients.

The 2 studies of the Space GlucoseControl system and the 5 studies of the eMPC algorithm all focused on outcomes relating to blood-glucose control. None was designed to look into clinical consequences such as morbidity and mortality outcomes, although in 1 study of the system the mortality rate was reported (Amrein et al. 2014).

In the trial by Cordingley et al. (2009), 1 of the 2 centres was based in London. None of the other studies was done in an NHS setting.

Relevance to NICE guidance programmes

The use of the Space GlucoseControl system is not currently planned into any NICE guidance programme.

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Search strategy and evidence selection

Search strategy

1. Databases were searched from inception to August 2014. The following keywords were used for the searches: Model Predictive Control Algorithm; Space Glucose Control; Space GlucoseControl; enhanced Model Predictive Control; eMPC; intensive care; critical care; ICU. The number of citations found is in brackets after each database:

   Medline (via OVID) (36); Embase (via OVID) (36); MEDLINE(R) In-Process & Other Non-Indexed Citations (via OVID) (12); Cochrane Library (total 222 including: 167 Cochrane reviews, 19 Trials, and 19 Economic evaluation); CAB Abstracts (8); Web of Science Science Citation Index (13).

   These citations were sifted through to find any relevant material, using the inclusion criteria below.

2. ClinicalTrials.gov, WHO ICTRP, and Current Controlled Trials were also searched for ongoing trials.

3. Information provided by the manufacturer in supporting this briefing was checked to identify any further information.

4. The manufacturer's website was thoroughly investigated.

Evidence selection

The inclusion criteria were as follows:

- Patients: critically ill patients in intensive care requiring tight glycaemic control
- Intervention: the Space GlucoseControl system, a computer-assisted device for glycaemic control, combining infusion pumps with an indication of dose level and timing derived from a propriety computer-based algorithm – the enhanced Model Predictive Control (eMPC) algorithm.

- Comparator: any other glycaemic control protocol. These include routine management, or any other computer-based algorithms.
- Outcomes: any relevant efficacy and safety clinical outcomes, including but not limited to:
  - blood glucose values
  - time to target range
  - proportion of time within target range
  - time within target range
  - number of hypoglycaemic and hyperglycaemic episodes
  - proportion of time spent below or above the cut-off levels for hypoglycaemia and hyperglycaemia
  - proposed next measurement time
  - insulin infusion rate
  - carbohydrate administration rate
  - hospital mortality and length of ICU stay
  - any adverse event
- Study design: for effectiveness – any comparative study; for other aspects of the device – any, including case reports.
- Only studies available in English language will be included.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers, and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not**

formal NICE guidance.

Development of this briefing

This briefing was developed for NICE by Birmingham and Brunel Consortium. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality assured and approved for publication.

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