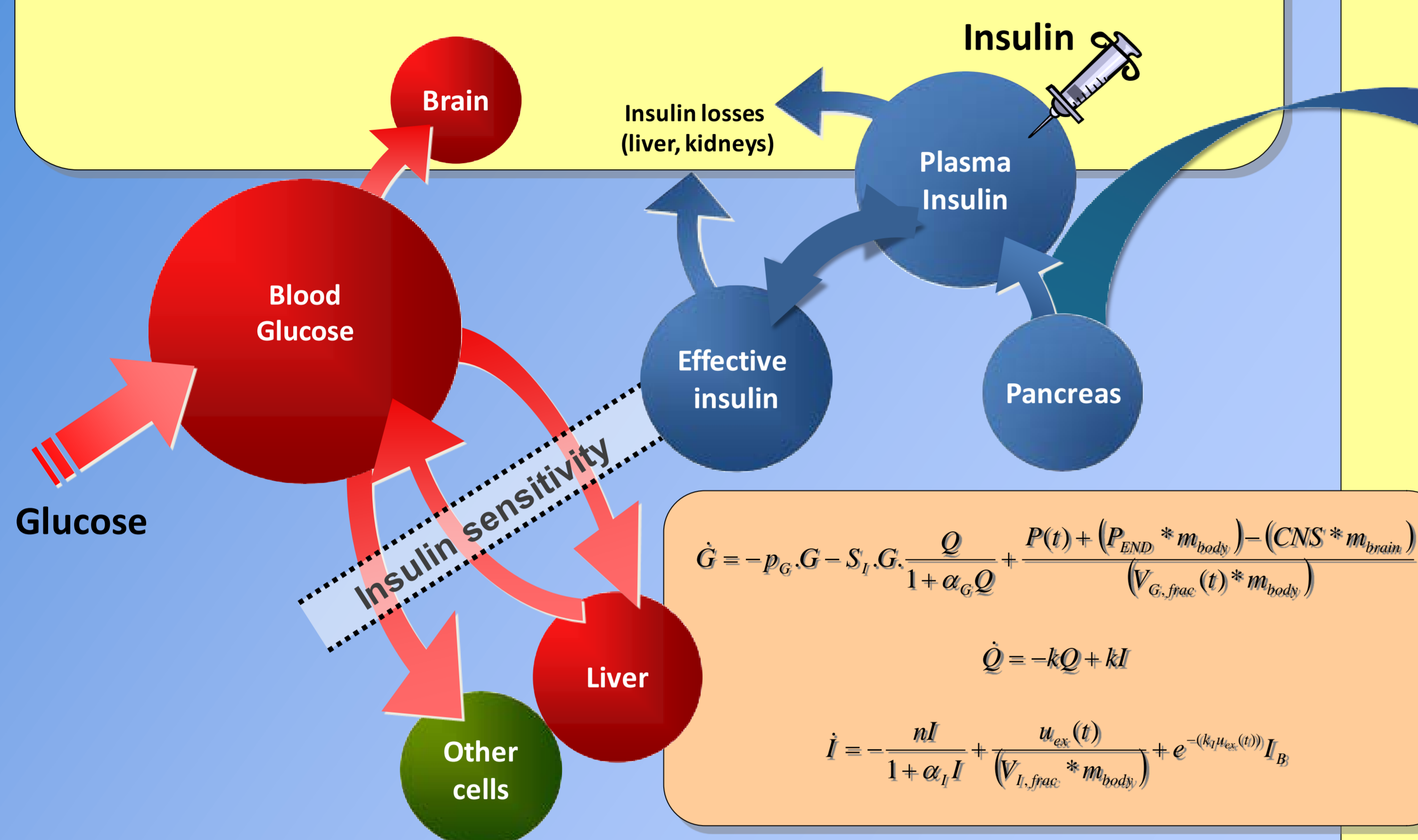# Accurate Glycaemic Control using a Stochastic TARgeted (STAR) Framework

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INTRODUCTION

Background: Accurate glycemic control (AGC) has proven difficult without excessive hypoglycemia risk. Stochastic TARgeted (STAR) glycemic control forecasts changes in insulin sensitivity to calculate a range of glycemic outcomes for an insulin intervention, creating a risk framework to increase safety and performance.

Objective: Create a new protocol with improved safety from hypoglycemia and reduced clinical burden using virtual trials, prior to clinical pilot trials.

$$\dot{G} = -p_G.G - S_I.G.\frac{Q}{1+\alpha_G Q} + \frac{P(t)+(P_{END}*m_{body})-(CNS*m_{brain})}{(V_{G,frac}(t)*m_{body})}$$

$$\dot{Q} = -kQ + kI$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{(V_{I,frac}*m_{body})} + e^{-(k_i u_{ex}(t))}I_B$$

METHODS

Clinically validated virtual trials on 371 virtual patients from the SPRINT AGC cohort were used to adapt the framework to Christchurch ICU. Model forecasts target control to a clinically specified glycemic range (80mg/dL to 145mg/dL). Measurement intervals of 2-3 hours were used when predicted 5th and/or 95th percentile BG were within target range.

Robustness to measurement error limit insulin increases to +2U/hour (max 6U/hour bolus and 3U/hr infusion) and nutrition changes to ±30% (between 30-100% of ACCP goal) per intervention.
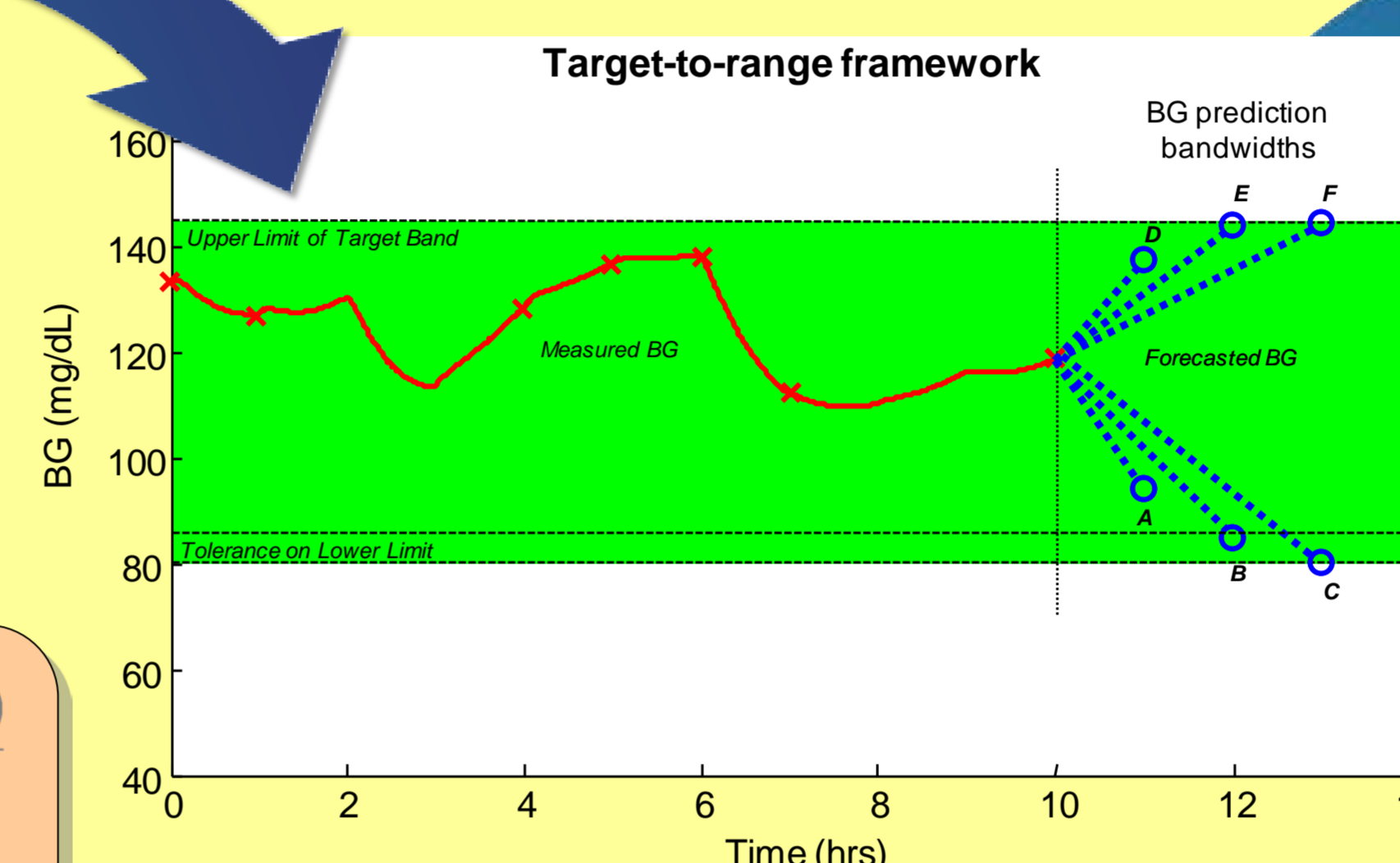
Fig. 1 (above): Controller forecast schematic for BG a target range of 80 – 145mg/dL. A BG measurement has been taken at 10hrs, and forecasts of BG have been generated (points A-F). The depicted distribution indicates the skewed nature of BG forecasts within the 5th-95th percentiles.
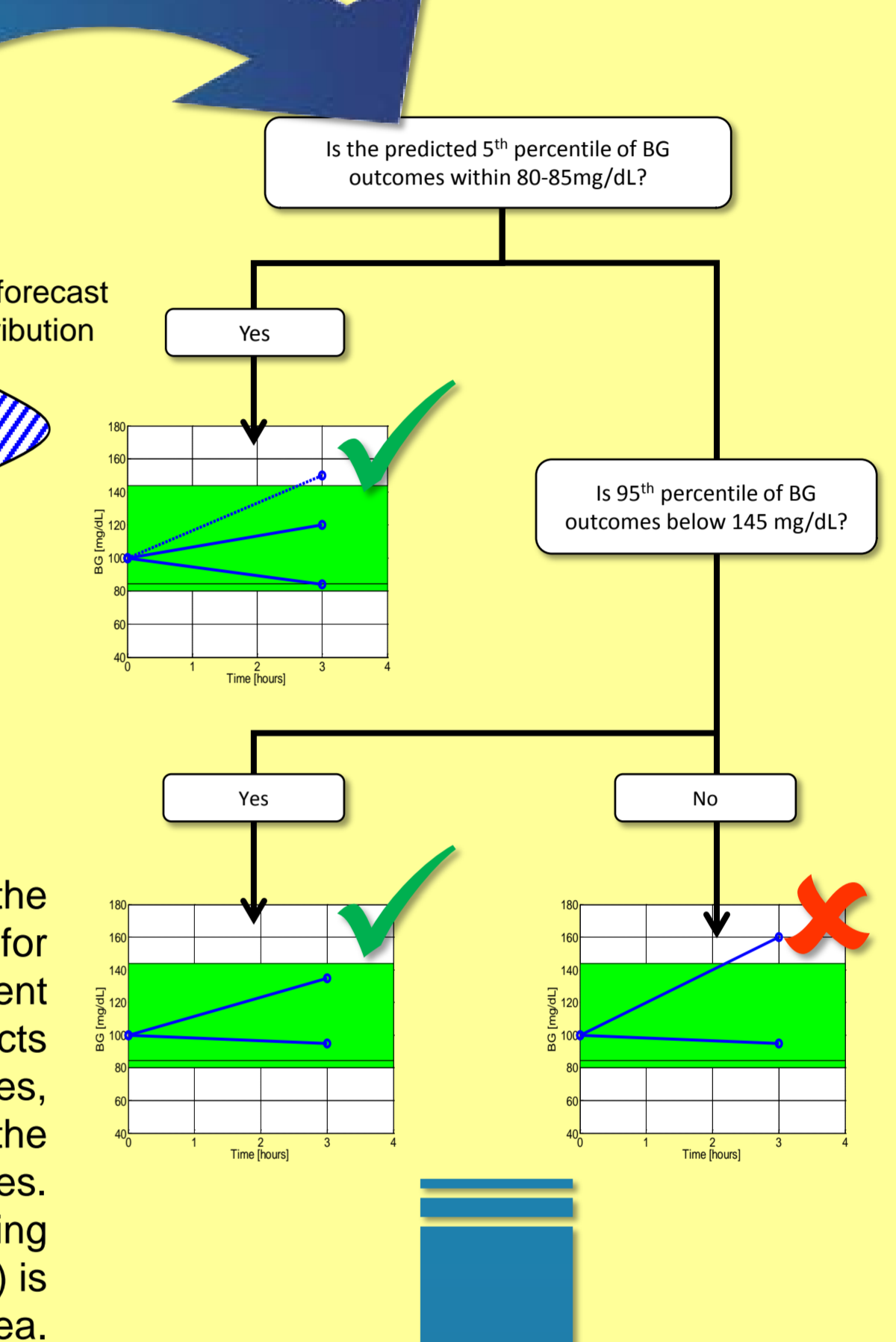
Fig. 2 (right): Selection logic for the possible forecasts possible for treatments at a 3-hourly treatment interval. The lower blue line depicts the 5th percentile of BG outcomes, and the upper blue line depicts the 95th percentile of BG outcomes. Target glycaemic range (including tolerance on the lower bound) is indicated by the green area.
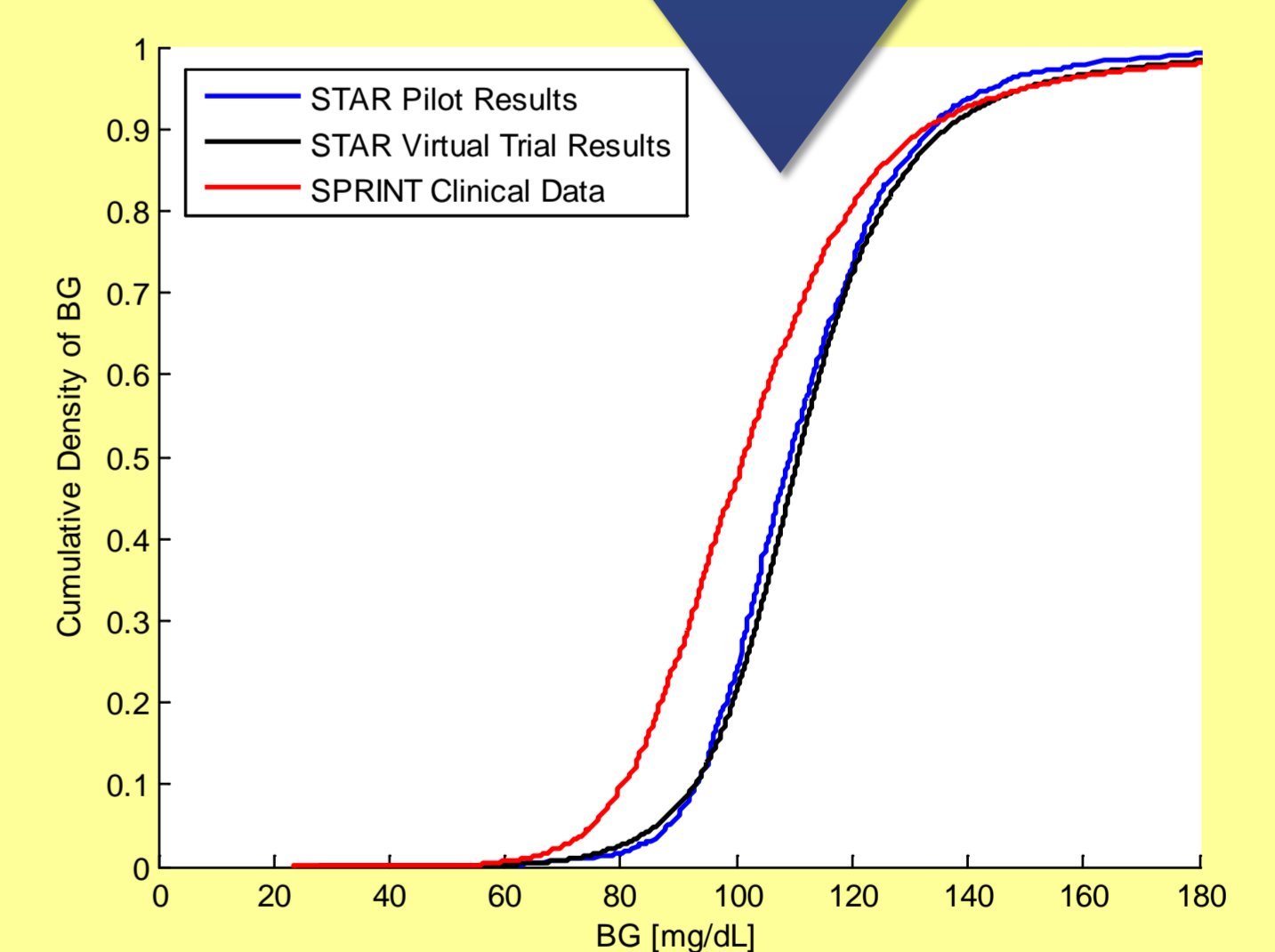
STAR DEVELOPMENT

Results: Severe hypoglycemia was reduced from 14 patients (clinical SPRINT data) to 6 with a simultaneous 23% workload reduction from 26,646 BG measurements to 20,050. Moderate hypoglycemia was reduced from 2.89% to 0.97%. Whole-cohort %BG in 80-145mg/dL was 91.0% (86.0% for SPRINT) and enteral nutrition was increased overall by 21% in median amount.

Fig. 3: STAR (right) and SPRINT (below) insulin/nutrition combination frequency. The distributions of insulin/nutrition rates selected by each protocol showed markedly different approaches to glycemic regulation. SPRINT used relatively constant insulin rates and adjusted nutrition. STAR aims to maximise nutrition input and uses a wider range of insulin rates to handle dynamics of more variable patients.
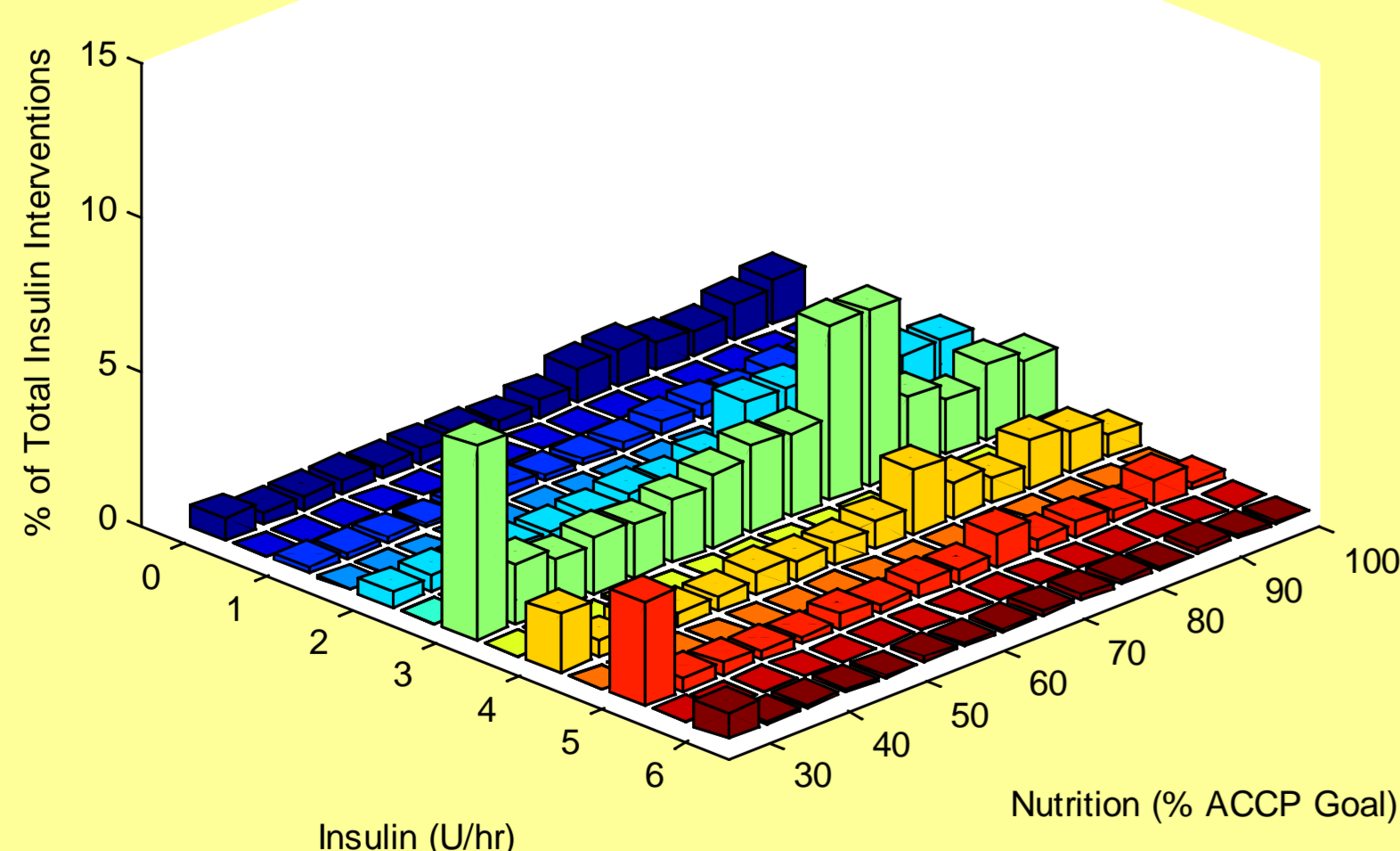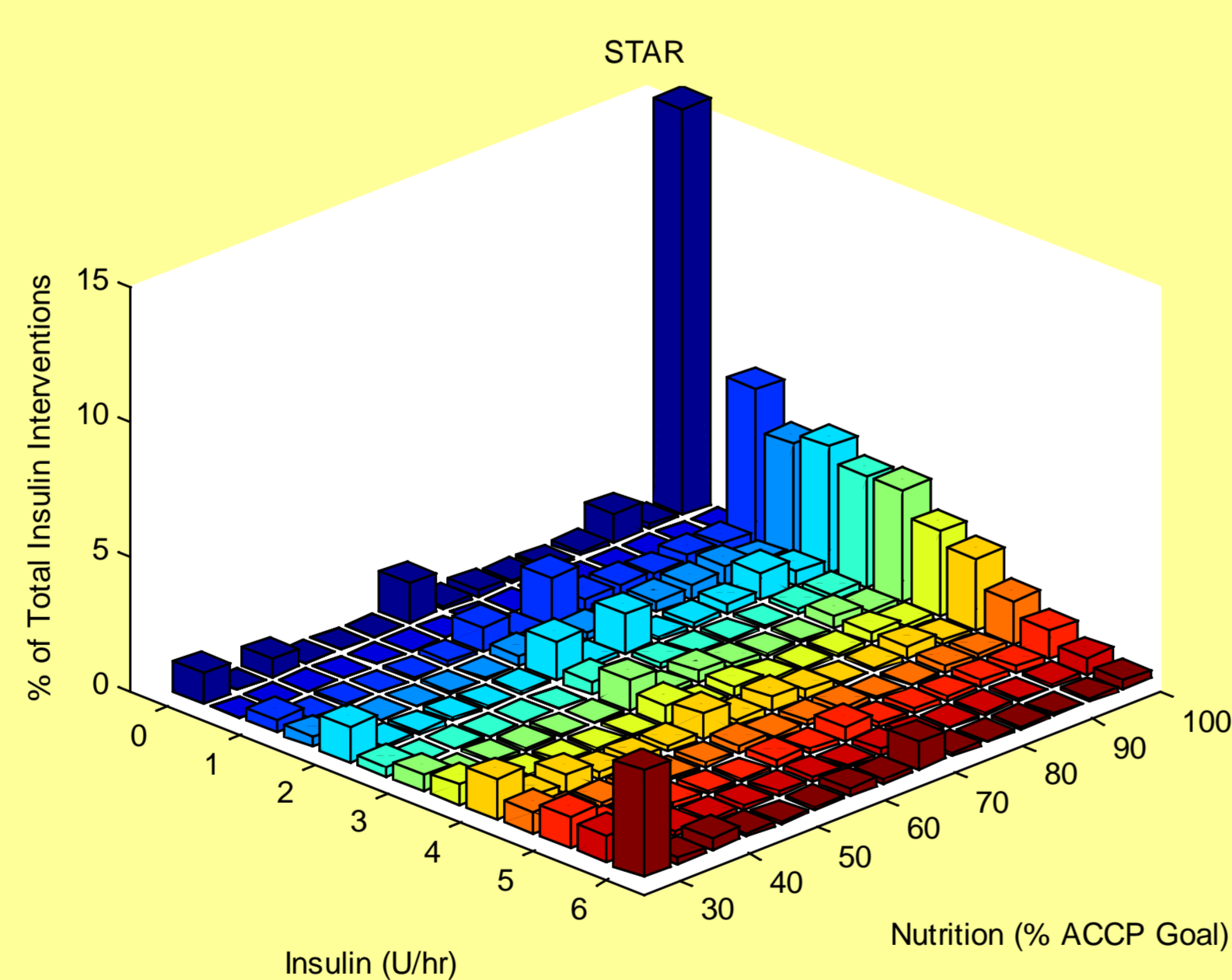
PILOT CLINICAL TRIALS

Clinical BG results over 10 pilot patients matched simulation results 93.4% of BG within 80-145mg/dL. Safety was maintained with 0.95% of BG < 72mg/dL and no severe hypoglycaemia events (BG < 40mg/dL). Median BG was 109 mg/dL [IQR: 101-121 mg/dL] versus simulated 111 mg/dL [IQR: 102-122 mg/dL], which matches very closely with the location and spread of BG in virtual trials.

CONCLUCISONS

Safe, accurate glycemic control that also reduces clinical effort is achieved using stochastic forecasting of potential patient variation. Initial pilot clinical trials matched simulation expectations and are ongoing.

	STAR	SPRINT Data
Workload		
# BG measurements:	20,050	26,646
Measures/day:	12.0	16.1
Control performance		
BG median [IQR] (mmol/L):	111 [102 - 122]	101 [90 - 115]
% BG within 80 - 145 mg/dL	91.0	86.0
% BG > 180 mg/dL	1.7	2.0
Safety		
% BG < 72 mg/dL	0.97	2.89
% BG < 40 mg/dL	0.02	0.04
# patients < 40 mg/dL	6	14
Clinical interventions		
Median insulin rate (U/hr):	2.5	3.0
Median glucose rate (g/hour):	5.0	4.1

Table 1: STAR simulation results indicated significant improvements over SPRINT. Workload reductions result from permitting 3-hourly treatment intervals enabled by BG forecasting capability to manage safety from hypoglycemia over the longer intervals. Median glucose administration rates were increased over SPRINT for greater clinical acceptance and insulin usage was balanced to maintain overall BG control performance.