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This project has received funding from the European Union's Horizon Europe Programme

DIABETES MELLITUS - EASA.2022.C20

D2.1 Analysis of the suitability of diagnostic tests

An Agency of the European Union

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DELIVERABLE NUMBER AND TITLE: **D-2.1** Analysis of the suitability of diagnostics tests
CONTRACT NUMBER: EASA.2022.C20
CONTRACTOR / AUTHOR: MUG
IPR OWNER: European Union Aviation Safety Agency
DISTRIBUTION: Public

VERSION CONTROL:

Version		Remarks
V0.1	Julia Mader 07.12.2023	submitted 07.12.2023
V0.2		updated version, submitted 04.04.2024
V0.3		updated version, submitted 11.06.2024
V1.0	Approved for publication	EASA approval for publication

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1. Review of the literature for best practice available diagnostic methods to evaluate long-term diabetes control

1.1 Introduction

This report provides the ways in which diagnostic measures (tests) are used to monitor blood glucose in individuals day to day to prevent significant variability of blood glucose through the day, and over longer periods to give an indication of overall blood glucose control.

1.2 The long-term goal of glycaemic monitoring to prevent secondary complications

Glycaemic control is the cornerstone of type 1 and type 2 diabetes management.[1,2] The chronic complications of diabetes are largely attributable to hyperglycaemia where there are longer than normal periods of raised blood glucose. The benefit of good glycaemic control to prevent secondary complications was demonstrated in the Diabetes Control and Complications Trial (DCCT), a prospective, randomized, controlled trial of intensive [mean HbA1c approximately 7% (53 mmol/mol)] versus standard [mean HbA1c approximately 9% [75 mmol/mol] glycaemic control performed in patients with type 1 diabetes (DM1). In this study improved glycaemic control was associated with 50–76% reduction in rates of development and progression of microvascular complications (diabetic kidney disease, neuropathy, retinopathy).[3]

Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown that these microvascular benefits last for at least twenty years.[4] Therefore, a target HbA1C of <7% (53 mmol/mol) is advised to prevent microvascular and macrovascular complications, in accordance with American Diabetes Association (ADA) and International Society guidelines for Diabetes in Adolescents.[1] To achieve a target HA1C of <7%, target blood glucose levels are approximately 70 to 144 mg/dL (4 to 8 mmol/L) before meals and 70 to 180 mg/dL (3.9 to 10 mmol/L) in total. The incidence and subsequent severity of secondary complications can produce symptoms and/or pathology that cause functional impairment (eg retinopathy) or increased incapacity risk (coronary artery disease).

1.3 The short-term goal of day to day glucose monitoring to achieve normoglycaemia

People with diabetes should have a target range of glycaemia in order to maintain a normal life, with reduced risk of hypoglycaemia or hyperglaycaemia, both of which can cause acute or subacture impairment. Glucose monitoring makes it possible to intervene in a timely manner with rising and falling glucose levels in order to obtain the above mentioned target blood glucose levels and prevent (principally) hypoglycaemic events. Monitoring is associated with improvements in glycaemic control when the patient and medical advisers use this information to make appropriate dietary or therapeutic adjustments.[5]

In the aviation context, is is extremely important to avoid incapacity due to low or high blood glucose. Symptoms and awareness can only give an indication of blood glucose levels and are generally variable and cannot be wholly relied upon to maintain safe awareness. People whose blood glucose levels are poorly controlled are more likely to gradually lose their awareness of hypoglycaemia (i.e. the warning symptoms) and therefore have an increased risk of hypoglycaemia.

1.4 Methods for monitoring of glycemic control

Monitoring glycaemic control consists of the following main methods [1] which are further detailed in Table 1:

- Self-monitoring of Blood Glucose – Regular glucose measurements (blood or interstitial) are used to monitor blood glucose levels and to adjust insulin dosage and carbohydrate intake. These measurements can be performed by capillary finger prick or measurement with a continuous subcutaneous glucose monitoring (CGM) device.

- Continuous glucose monitoring (CGM) devices measure interstitial fluid glucose levels which correlate well with plasma glucose, with glucose levels measured every 1 to 5 minutes

- Haemoglobin A1c – Haemoglobin A1c (A1C; also called blood glycated haemoglobin or glycohaemoglobin) is used to indicate medium-term average glycaemic control over 60 - 120 days.

Self-Monitoring of Blood Glucose (SMBG)

Self-monitoring of blood glucose (SMBG) with a blood glucose meter requires a small blood sample (0.3 to 1 microliter), obtained via a finger prick. Lancet devices are available, which can be of ultra-fine thickness; others contain multiple lancets for easy and safe use.[6]

Frequency of finger-prick glucose monitoring:

For people using SMBG home testing should be performed at least four times per day (before meals and at bedtime), occasionally postprandial (90 to 180 minutes after meals), before exercise and in special situations.[6] The frequency of testing may vary based on individual needs.

Self-Monitoring of Blood Glucose (SMBG): standards

There are several current standards for the accuracy of blood glucose meters, but the two most commonly used, and those which provide the most accurate and reliable data for diabetes management, are those of the International Organization for Standardization (ISO) (ISO 15197:2013) (95% within 15% for BG ≥100 mg/dL 95% within 15 mg/dL for BG <100 mg/dL; 99% in A or B region of consensus error grid) and the Food and Drug Agency (FDA). In Europe, monitors currently marketed must meet current ISO standards. In the US, currently marketed monitors must meet the standard under which they are approved, which may not be the current standard. Additionally, monitoring flow accuracy is left to the manufacturer and not routinely checked by an independent source.

BGM devices and performance

The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for blood glucose monitoring (www.diabetestechnology.org/surveillance/). One analysis found that only 6 of the top 18 glucose meters met the accuracy standard.[9] There are single-meter studies that have found benefits with individual meter systems, but few studies have compared meters head-to-head.[10]

Continuous glucose monitoring (CGM)

Continuous glucose monitoring (CGM) devices measure interstitial fluid glucose levels which correlate well with plasma glucose, albeit with a 5 to 10 minutes delay. Depending on the device, glucose levels are measured every 1 to 5 minutes.

Most CGM devices access the interstitial fluid through an electrochemical enzymatic sensor that is inserted subcutaneously and replaced every 7 to 14 days. Glucose readings are automatically sent to a device-specific receiver, smartphone/watch or other smart device.[7] On the other hand, a single fluorescence-based sensor can be implanted subcutaneously by a healthcare provider.[8] A transmitter (placed on the skin) is attached to the sensor (or worn over the sensor) and transmits the glucose data to a receiver/smartphone. With this device, the implanted sensor must be replaced after 90 to 180 days.

CGM systems provide visualization of the current glucose level as well as a trend arrow analysis, which indicates the direction of changing glucose. This technology is very valuable and can help patients refine insulin dosing in a timely manner.

Many CGM systems are now available on the market. With technology advancing so rapidly and both accuracy and reliability improving with each new generation it would not be possible to compare each available device.

The requirements for the pilots and ATCOs

It is essential that pilots and ATCOs ensure that they use a glucose meter or CGM device that meets the required standards and it is good practice to carry a spare meter during flying or controlling in case the usual meter becomes faulty (which is a rare case).

The core difference between these two devices is that a CGM takes a reading from interstitial fluid, while a finger prick test uses a blood sample. To truly get the best situational awareness of blood glucose levels is to use a CGM device and reference it with a blood glucometer. The fingerprick method gives a standalone value, but as well as also giving a current value, the CGM devices give a rate and direction of change. This is akin to the pilot knowing his/her altitude above ground, and whether they are climbing or descending and by how much.

Therefore, the use of CGM in combination with fingerprick testing by ITDM pilots holding a class 1 or 2 certificate and ATCOs would greatly improve the practicability and safety of glycaemic control while on duty. The improvements in CGM glucose sensor technologies are a major advance in the past decade or so (and particular since the origin of the ARA.MED.330 protocol). CGMs provide real-time data and help to make informed short term and medium-term treatment management decisions. Depending on the type of the sensor, they can provide both a glucose trend and a warning, and can therefore be very helpful during flight and controlling duty periods.

Furthermore, CGMs provide an effective method to share results with aeromedical examiners and treating physicians in order to get timely medical advice concerning glycaemic management.

Ease of use whilst flying or controlling is also very important. In the duty period of an air traffic controller it is likely that they will be indoors and in an office-like environment where the devices are being placed on a desk or workstation area for use. In the flight environment, there are substantial differences, for example between an open-cockpit aircraft and the ‘office-like’ arrangement of a modern large jet aircraft. This is one of the reasons why the original UK and subsequent protocols have required a medical flight test to be conducted, for the pilot to prove that he/she can undertake tests whilst maintaining control of the aircraft (some obviously without an autopilot). From the UK experience in the early days of the protocol development and with the UK National Private Pilots’ Licence (NPPL), it was evident that pilots were very resourceful in managing their testing equipment, often with the use of knee pads and similar items as well as Velcro tape to secure the devices. With the increasingly common use of CGMs for inflight monitoring, this is considerably easier as all that is needed is access to the device or watch that provides the visual readout.

The guidance for the timing of glucose testing was also considered in relation to device usage and the operational tasks. The busiest times for pilots are during the take-off and departure and the descent and landing. For this reason 30 minutes before take off and 30 minutes before landing (“top of descent”) were used as a convenient (low-workload) time before the critical stages of flight (higher workload) and also at a time when the manoevering /control of the aircraft was low. During development of the protocol, it was demonstrated that a small helicopter could be flown easily and safely by a pilot experienced in flying, but not in fingerprick testing, to test while flying in the circuit at a small aerodrome.

An additional safety measure was introduced with the protocol: If a test was missed due to operational or emergency reasons, ingesting 10-15 mg of glucose (e.g., sweets) could delay the required test by up

to 39 minutes, allowing the flying task to be completed without further complications. While the use of CGMs reduces the need for this measure somewhat, consuming a small but meaningful amount of glucose can mitigate developing hypoglycemia without significantly affecting the rarer situation of evolving hyperglycemia.

1.5 Conclusion

Good glycaemic control is the cornerstone of diabetes management and the key to preventing acute incapacity risk and delaying microvascular complications which lead to premature morbidity and mortality. CGM devices that meet the ISO standard alongside occasional finger-stick monitoring for verification purposes is considered the gold standard in achieving effective glycaemic control.

Pilots and ATCOs granted medical certificates to work within the aviation industry would grately benefit from the use of CGM devices during operational tasks because of the trend arrows and alerts which provide a forecast of changing glucose concentration and enable the user to take action to mitigate dangerously low or high glucose levels. SMBG has proved to be a safe method of enabling insulin-treated pilots to fly. However, a study comparing a modern CGM system to SMBG while flying is currently underway as part of the Horizon project studies, the results of which will provide evidence as to the safe use of CGM within the cockpit.

Table 1: Summary of Diagnostics Methods and Monitoring of Glucose Control [11]

Method	Pros	Cons	Use Within the Aviation Industry
Fasting plasma glucose (FPG)	• Quick and simple test to diagnose diabetes • Biological variability of plasma glucose can reveal disturbance within days • Much cheaper to perform than 2-h OGTT and A1c • Readily available in most countries worldwide	• Snap shot of glucose at the time the sample is taken so can miss hypoglycaemia and hyperglycaemia • Does not capture chronic hyperglycaemia or post-prandial glucose peaks • Must be a fasted sample so require the individual to be appropriately prepared • Acute perturbations (e.g. stress, diet, exercise, smoking) can affect FPG • Poor marker of future CVD events	Can be used for diagnosis by all pilots and ATCOs
2-hour oral glucose tolerance test (2-h OGTT)	• Catches information about fasting glucose states as well as post-prandial hyperglycaemia • Stronger predictor of cardiovascular disease than A1c	• More time consuming for patient, healthcare professional and laboratory resources • Oral glucose drink needs to be standardised for results to be transferrable between centres/countries • Does not capture chronic hyperglycaemia • First sample must be a fasted sample so require the individual to be appropriately prepared • Acute perturbations (e.g. stress, diet, exercise, smoking) can affect 2-h OGTT • More expensive than FPG	Recom-mended by the ICAO for diagnosis by all pilots and ATCOs [12]
Plasma HbA1c	• Equivalent of 1000's of FPG measurements • Captures post-prandial peaks and chronic hyperglycaemia • Microangiopathic complications are associated with HbA1c	• Does not tell you about daily glucose variability • Does not provide insight into hypoglycaemic events or post-prandial hyperglycaemia • Biological variability of A1c is lower than FPG and 2-h OGTT	Can be used for diagnosis and monitoring of glycaemic control by pilots of all classes and ATCOs

	• Better related to cardiovascular disease than FPG • Fasting not needed • No accurate preturbations (e.g. stress, diet, exercise, smoking) affect A1c • Greater pre-analytical stability than FPG • Can be used concomitantly for diagnosing and directing glucose management	• Standardisation of A1c assay is poor, even in Western countries, and standardisation of glucose assay would be easier to implement • A1c is unreliable in many subjects especially erythrocyte turnover rates e.g. anaemia, malaria, haemoglobinopathies, blood loss, pregnancy, uraemia, haemolysis etc • A1c has significant differences in various ethnic groups and ages which are poorly understood and characterised • Need to wait 120 days for biological variability of glucose to reveal disturbance in glucose metabolism • More expensive than FPG • A1c not available in many countries • A1c levels of 6.0-6.5% do not predict diabetes as effectively as FPG and 2-h OGTT • Sensitivity to detect diabetes defined by 2-h OGTT is <50% thus the majority of individual will remain undiagnosed/have a delay in their diagnosis	
Finger-stick capillary blood glucose monitoring (SMBG)	• Most accurate method for determining plasma glucose concentration • Gives you an instant idea of glycaemic control at that moment in time • Relatively quick and simple to perform • Can be performed by a third party	• More time consuming to perform than using CGM systems • More equipment needed to obtain a reading • Requires the use of both hands to peform the test • Draws blood which can be problematic in certain environments/risks contamination of surroundings	Current gold standard for monitoring of glycaemic control during duty periods by pilots of all classes and ATCOs. However, use of the testing machines during solo flight in light aircraft can be a

		• Causes pain to the user each time a measurement is performed • Not always able to wash hands prior to testing which may affect accuracy • Contaminants on the skin surface can interfere with the accuracy of the result • Susceptible to user error depending on technique • Inadequate blood sample may mean repeated tests • Only gives you a snapshot but no information about which directions glycaemic control is heading • Readings only as useful as the frequency with which they are performed	challenge and should be practiced and assessed before permitting flight without a safety pilot.
Intermittently-Scanned Contionuous glucose monitors (is-CGM)	• Provides information about the immediate glucose level • Provides a more accurate picture of glucose levels throughout the day by visualising trends • Newer models include alerts when glucose levels are rising or falling to reduce hypoglycaemia and hyperglycaemia • Some models have arrows to show the direction and speed with which glucose concentration is changing • Some provide basic statistical information on overall control as well as for specific times of day/day of week • Can be scanned by third party if needed	• Measure interstitial fluid which lags behind serum glucose concentration by 5-10 minutes • Rely on Bluetooth/phone signal so may not work in certain geographical locations • Only as useful as the number of times the device is scanned – user needs to remember to scan the device • Unable to obtain nocturnal data as need to wake up to scan the device • The devices do not have alert or alarm features when glucose levels are rising or falling • Can be more expensive than finger-stick monitoring devices depending on the	Can be used in addition to SMBG for monitoring of glycaemic control during duty periods by pilots of all classes and ATCOs Much easier to use in flight as fewer parts and less complexity of operations required to get a reading

	• Sensors stay insitu for around 2 weeks so significantly less needle pricks compared to SMBG • Overall much less waste produced than SMBG • Do not need to carry sharps bin around with testing equipment • Able to swim, shower, exercise as normal with the sensor, no restrictions on daily life	number of SMBG tests per day • Potential risk of a reaction to the adhesive used • Constant presence of the sensor on the body risking potential infection and stigma • Risk on infection due to sensor remaining insitu • Unable to share data with family or healthcare teams	
Real-Time Continuous glucose monitors (rt-CGM)	• Automatically provides a constant stream of glucose data throughout the day and night • Obtains nocturnal data without the user needing to wake to test • Identifies episodes of hypoglycaemia unawareness • Data can be visualised in numerical and graphical form • Gives an accurate picture of past and present glucose trends • Trend arrows to show the direction and speed with which glucose concentration is changing • Predict future change in glucose concentration for the next 2 hours • Provide alerts and alarms when glucose levels rising or falling to prevent hyper- and hypoglycaemia • In depth information into the number, severity, frequency and cause of hypoglycemic episodes • Provide basic statistics to give information on overall control as well as for specific times of day/day of week	• Measure interstitial fluid which lags behind serum glucose concentration by 5-10 minutes • May require calibration with finger-stick glucose • Can be more complicated to learn how to use it • Can be more difficult to insert the sensors for people with manual dexterity difficulties • Rely on Bluetooth/phone signal so may not work in certain geographical locations • The reader or phone must be within a certain distance of the transmitter to receive data • More expensive than finger-stick monitoring devices • May cause information overload • Can cause alarm fatigue, especially at night which can also affect others e.g. partner • Potential risk of a reaction to the adhesive used • Constant presence of the sensor on the body risking potential infection and stigma	Can be used in addition to SMBG for monitoring of glycaemic control during duty periods by pilots of all classes and ATCOs Much easier to use in flight as fewer parts and less complexity of operations required to get a reading

	• Show how lifestyle choices and other factors affect glucose • Data sharing options with family provides additional safety feature and with physicians to enable improved diabetes management • Data can be viewed on a receiving device, smart watches and compatibale smartphones • Sensors stay insitu for 10-14 days so significantly less needle pricks compared to SMBG • Overall less waste than SMBG • Do not need to carry sharps bin around with testing equipment • Able to swim, shower, exercise as normal with the sensor, no restrictions on daily life • Can be integrated with an insulin pump and insulin delivery can be automatically paused or adjusted in response to changes in glucose levels	• Potential for sensor or transmitter failures	

*It should be emphasized that any comparison of A1C with FPG or 2-h OGTT is equivocal because a true gold standard is not available.

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2. Glucose monitoring methods and performance at altitude

Abstract

Introduction

Pilots with diabetes are legally required to monitor their blood glucose levels regularly during flights. This is achieved through capillary glucose measurements, which may make assessments quicker. The use and accuracy of Continuous Glucose Monitoring (CGM) technologies at altitude remain understudied. This study assessed the use of CGM compared to plasma glucose and self-monitoring blood glucose (SMBG) during simulated flights.

Methods

This observational study is conducted on Class 1 and Class 2 pilots with diabetes who were recruited from the SUNDIF trial under the EASA Horizon Europe Work Programme 2021-2022. Inclusion criteria included: diagnosis of type 1 diabetes, diagnosis must be greater than 12 months, currently on insulin pump therapy, aged between 18-65 years, Body-Mass-Index of <30 kg/m^2,HbA1c of <9%, able to undertake long haul airliner flight, and does not suffer from any cardiovascular, respiratory, or ENT diseases. Glucose measurements were taken from pilots during both fasted and postprandial states at both ground level and during a simulated flight protocol in a hypobaric chamber. Flight protocol simulated a 20-minute ascent to 8,200 feet equivalent altitude, 190-minute cruise (550 mmHg), and a 20-minute descent to the ground (750 mmHg). Three CGM and two SMBG were used to monitor interstitial and capillary glucose levels throughout the study, and venous blood samples were taken to determine plasma glucose concentration. Data was extracted and recorded by investigators during study.

Results

Six pilots with insulin-dependent diabetes were studied. All participants were male, with a median age of 40 (ranged 20-61), height of 179 cm (ranged 169-184cm), and weight of 83.7 kg (range of 75.1-101.9 kg). Flight-associated atmospheric pressure changes did not result in a significant difference in CGM measurements compared to ground level, with Pearson correlation ranges of 0.73-0.94 and 0.68-0.96 respectively.

Conclusion

The results of this study show that CGMs and capillary measurements are comparable across flight-associated atmospheric pressure changes. As measurement cannot be altered, the tested measurement devices were suitable for diabetes care-based decisions.

2.1 Introduction

Management challenges aside, people with diabetes also face discrimination and prejudice in their work lives. The risk of hypoglycaemia and incapacitation is the leading reason for blanket-ban policies to bar people with insulin-treated diabetes from engaging in safety-critical occupations[1]. This has led to the development of the International Charter of Rights and Responsibilities of People with Diabetes by the International Diabetes Federation[2]. The charter's aims were to reduce barriers for these members to participate in society while balancing public safety. Since 2011, further advances in insulin analogues, insulin pumps, and non-invasive Continuous Glucose Monitoring (CGM) systems have greatly improved glycaemic control in insulin-treated diabetes[3]. These developments have effectively reduced severe hypoglycaemic events and diabetes-related comorbidities and, hence, warrants further review of currently accepted safety practices. Aviation has traditionally led these changes within safety-critical industries and have introduced various safety protocols for insulin-treated pilots.

Blood glucose monitoring is usually performed using a 'finger-prick' and a hand-held device, commonly referred to as Self-Monitoring of Blood Glucose (SMBG). This is used in both type 1 and 2 diabetes, with

insulin-treated users having to perform multiple SMBGs daily. CGMs are increasingly common and relies on disposable sensors and transmitters that measure glucose levels of interstitial fluid via a small cannula. Through CGMs, users can now better manage their diabetes using real-time values and trends on glucose levels. This has both been well-received by users and shown to improve overall glycaemic control, reduce glucose variability, and increase time in range in insulin-treated diabetes[4–7].

The importance in determining the safety and reliability of CGM under frequent atmospheric pressure changes, as experienced during flights, cannot be understated. For its effective adoption within aviation, the performance of these devices on flights should be comparable to its ground level performance. Our group has completed a preliminary study on Dexcom G6® during flights and shown CGM as a credible alternative to SMBG[8]. This further study aims to compare glucose measurements of CGM, SMBG, and blood plasma between ground level and simulated altitude changes during flights.

2.2 Methods

Simulated Flight Protocol and Meal Test

This study was conducted as part of the SUNDIF trial, where participants ingest a standardised meal at both ground-level and simulated flight. A hypobaric chamber was used to replicate the cabin pressure changes over short flights. Commercial aircraft operate at a cruising altitude of 40,000 feet, and cabins are pressurised at approximately 8,200 feet (550 mmHg).

The protocol consists of the following phases in chronological order: 30 minutes of ground level (750 mmHg), ascent to 8,200 feet (550 mmHg) over 20 minutes, 30 minutes of cruising altitude (550 mmHg), descent to ground level (750 mmHg) over 20 minutes, and then 30 further minutes of ground level pressure. Cabin pressurisation of more than 8,000 feet was chosen to include the extremes of normal operations[9]. A 20-minute ascent/descent was selected to represent a normal flight, as the rate of cabin pressurisation may vary with aircraft, route, target altitude, and climbing pattern. All CGM sensors and transmitters used were designed for operations at least >10,000 feet altitude[10–12].

As part of the SUNDIF trial, participants fasted, received a glucose infusion, and ingested a standardised meal with ^{13}C glucose during the study. Participants also self-administered insulin per their carbohydrate counting regimen. The same meal, glucose infusion, and insulin dose were replicated across both test settings.

Inclusion criteria for the SUNDIF trial included: diagnosis of type 1 diabetes, diagnoseis must be greater than 12 months, currently on insulin pump therapy, aged between 18-65 years, Body-Mass-Index of <30 kg/m^2,HbA1c of <9%, able to undertake long haul airliner flight, and does not suffer from any cardiovascular, respiratory, or ENT diseases.

Measurements and Statistical Analysis

Participants were equipped with 3 different CGM systems: Dexcom G7, Guardian 4, and Libre Freestyle Flash. The Guardian 4 and Dexcom G7 CGM systems were real-time Continuous Glucose Monitors (rtCGM) whereas the Libre Flash was an intermittently scanned Continuous Glucose Monitor (isCGM). CGMs were applied the day prior to allow for their calibration, with each sensor placed in approximately the same location on each participants' arm or abdomen to minimise variation due to tissue differences[13]. Abbott Freestyle Precision Pro and ABX PENTRA were used for SMBG and plasma glucose measurements respectively. Glucose measurements from SMBG, CGM, and plasma were recorded for the following time points: -100, -50, -20, 0, 10, 20, 30, 60, 90, 120, 150, 180, and 210 minutes, with 0 representing the time of meal ingestion. All glucose measurements were extracted and recorded by investigators during study.

Measurements were collected and analysed using Microsoft Excel® by authors AM and KSF. Statistical analysis was conducted by author PB, using R statistical packages. Pearson correlation against plasma glucose was calculated for each glucose measurement modality.

2.3 Results

All six pilots participated in this study. All participants were male, with a median age of 40 years (ranged 20-61). A total of 156 plasma glucose, 156 SMBG, and 149 Libre capillary glucose data points were collected across the two settings. The CGM dataset included 153 data points for Libre Flash, 140 for Dexcom G7, and 89 for Guardian 4. Due to connection and calibration difficulties, not all SMBG/plasma glucose has a corresponding CGM measurement data point. No datapoints were discarded or deleted.

Pearson correlation showed strong to very strong correlation between both the SMBG and different CGMs against plasma glucose levels (**Table 1**). The correlation of each measurement modality against plasma glucose is plotted in **Figure 1**. The glucose measurements of each modality are plotted against each other for both ground and simulated flights (**Figure 2**). The Mean Absolute Relative Difference (MARD) of the aggregated data of CGM, SMBG, and plasma glucose measurements ranged between 12-17% (**Table 2**).

Table 1. The Pearson correlation of each measurement modality compared against plasma glucose across both ground and simulated flight conditions

Correlation with plasma glucose	Glucose Location	Ground		Simulated flight	
		Pearson Correlation	Number of data points	Pearson Correlation	Number of data points
SMBG	Capillary	0.96	78	0.94	78
Libre Capillary	Capillary	0.92	74	0.92	75
Dexcom G7	Interstitial Fluid	0.82	64	0.85	76
Guardian 4	Interstitial Fluid	0.68	37	0.73	52
Libre Flash	Interstitial Fluid	0.95	78	0.88	75

SMBG: Self-Monitor Blood Glucose

Figure 1. Glucose levels of ground and simulated flights plotted against plasma glucose measurements. A) Self-Monitor Blood Glucose (SMBG) capillary glucose, B) Libre capillary glucose,
C) Libre Flash Continuous Glucose Monitoring (CGM), D) Guardian 4 CGM, and E) Dexcom 7 CGM. Simulated Flight is depicted by closed/black circles and ground-level atmospheric pressure open/white circles.

Figure 2. The mean glucose measurements of simulated flights (A) and ground/control (B) plotted against meal time. The controlled meal was given at 0 minutes.
SMBG: Self-Monitor Blood Glucose; Libre Cap: Libre Capillary

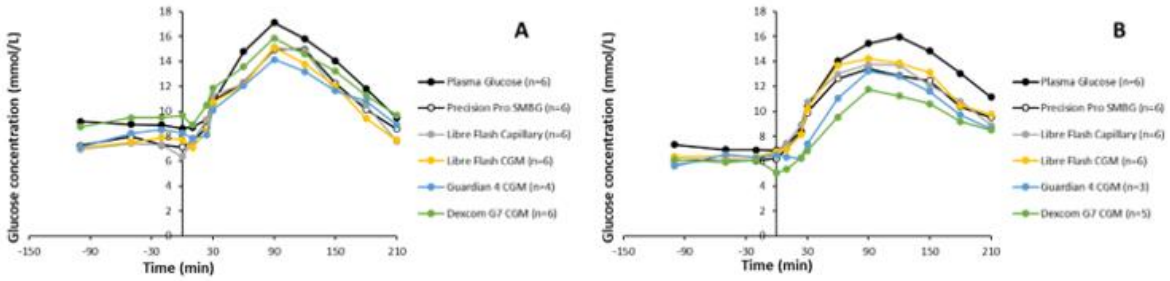

Table 2. Mean Absolute Relative Difference (MARD) calculations of aggregated glucose measurements of ground and simulated flight.

MARD Pair	Ground	Flight
Plasma - SMBG	13.47	14.13
Plasma - CGM	15.25	17.10
SMBG - CGM	11.63	17.76

MARD: Mean Absolute Relative Difference; SMBG: Self-Monitor Blood Glucose; CGM: Continuous Glucose Monitoring

2.4 Discussion

Our findings demonstrated that all glucose measurement modalities had strong to very strong correlations with the plasma glucose. Furthermore, the correlation strengths of both ground and simulated flight conditions remained similar. This corroborates with our previous findings where pilots' Dexcom G6 CGM system showed very strong correlation (r=0.843, P<0.001) with SMBG measurements for both pre- and in-flight periods[8].

The highest correlation coefficients (r = 0.92-0.96) were of SMBG and Libre Flash, with both being direct capillary measurements. This is in line with literature, where the correlation coefficient of capillary glucose against plasma glucose ranges from 0.93 to 0.97[14,15]. With strong to very strong correlations in all the devices, emphasis should be placed on the difference in correlation between the environments. Although isCGM Libre Flash demonstrated the largest amount of difference in correlation coefficient (ground r = 0.95 vs flight r = 0.88), it remained very strongly correlated across both settings. Despite having fewer Guardian 4 data points available, it still demonstrated strong correlation at both ground and altitude (r=0.68 vs r=0.73; with n=37 and n=52 respectively). As users also use SMBG in-flights, our findings provide a like-for-like comparison against the gold standard used at high altitudes by taking into account the impact of altitude on SMBG devices. Our data show that CGM measurements closely correlates with SMBG and, therefore, can perform similarly across both in-flight and ground level environment. This supports the use of CGM as a viable alternative to SMBG at high altitudes.

MARD values of <10% are generally regarded to provide good analytical performance, and a review of trials reported most studies to be between 10 and 20%[16]. Our findings also lie within this range for both flight and ground. However, it is important to note that MARD will be impacted by the number of data points as most, including our study, evaluated a small number of users over several days. Very few examined >100 patients or multiple CGMs. Our findings showed close alignment of CGMs to each other and against plasma and capillary glucose. Additionally, as the CGM-plasma and CGM-capillary correlations remain similar across both settings, users can rely on and act upon CGM data as they would SMBG regardless of altitude.

Previously, Oberg and Fink reported that environmental changes, such as altitude, temperature, and humidity can cause both over- and underestimates of blood glucose measurements[17,18]. El Rifai *et al.* recently found similarly elevated MARD for Dexcom G6 CGMs on 6 participants at altitudes of between 10,000 and 14,000 feet[13]. They identified that there were no significant differences between MARDs of their lowest and highest altitudes, and similarly concluded that accuracy is not solely affected by altitude. They proposed that factors such as physical activity, temperature, lag between plasma and interstitial glucose readings, and rate of altitude change. Additionally, as identified in the study, the CGM measurements may also differ per sensor location and therefore, by applying the sensors to the same location across both visits would provide more accurate comparisons. Regardless, the aim of this study was to compare in-flight performance of CGMs against ground level, rather than obtain an objective measurement of its accuracy. With the accepted use of CGMs during free living, and its accepted performance relative to SMBG, the lack of significant identifiable deviation from SMBG measurements at altitudes support it as a viable modality within the aviation setting.

2.5 Limitations

The scope of this study is confined by the access to the hypobaric chamber and its physical size. Therefore, data points are limited by the number of participants studied. In line with the aims of this study to compare the effects of de-pressurisation on CGM performance, comparisons were made between corresponding measurements at ground level and simulated flights, comparisons. This simulated cabin pressures of this study does not exceed 8,200 feet equivalent and therefore the findings may not be representative of rapid/emergency decompression scenarios. Additionally, as our simulated flight protocol was under 4 hours, it is comparable to flights within mainland Europe. However, our findings may be less applicable to long haul flights, therefore further studies are needed to explore the effects of longer periods of atmospheric pressure changes. The movements, vibrations and tasks associated with pilots' normal in-flight operations were not within the scope of the study. The CGMs were placed on participants' arms and were not more restricted than in typical flight environment. This may approximate the normal arm movements that pilots during flights. Future aviation simulation studies evaluating CGM performance against arm movements and placement location may provide additional understanding on how regular movements and vibrations can influence readings.

2.6 Conclusion

The modern CGM systems continue to provide vital support in the management of diabetes for insulin-treated individuals. Its uses may extend to overcoming occupational barriers, particularly for those operating in safety-critical industries like aviation. Our study found that CGM measurements demonstrate a strong to very strong correlation with SMBG and plasma glucose measurements across both ground-level environments and simulated flight conditions with lowered atmospheric pressures. As such, CGMs provide a viable alternative to SMBG within aviation settings.

After analyzing diagnostic measures for diabetes control as well as discussing modern CGM systems and showing their correlation with SMBG and plasma glucose measurements at ground-level environments and simulated flight conditions in the hypobaric chamber, we next want to have a look at what is known about safety and performance of measures for diabetes control in aviation in those countries where pilots with insulin-dependent diabetes are allowed to fly under certain protocols. This information from practical experience should not be ignored when talking about the suitability of diagnostic tests and possible changes in recommendations for future aeromedical requirements for medical certificates.

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Published data of people treated with insulin who are allowed to fly

Although several countries allow pilots to fly for leisure, no data have been published to evaluate the safety and the performance of any of their protocols (**Table 2**).

Table 2. Comparison of flying protocols

Protocol	Full clinical assess--ment	Mode of glucose monito-ring	Frequency of in-flight testing (minutes)	Monito--ring before landing (minutes)	Range of accept-ability whilst flying (glucose mmol/L)	HbA1c assess-ments	Compli-cation Surveil-lance	Published Data
Australia	Yes	Blood & CGM	60	30	5-15	3 monthly	-	No
Israel	Yes	Blood	120	30	>5.5	3 monthly	Yearly	No
Canada	Yes	Blood	30	30	6-15	6 monthly	Yearly	No
United Kingdom /Ireland/ Austria	Yes	Blood	60	30	5-15	6 monthly	Yearly	Yes
New Zealand	Yes	Blood & CGM	60	30	5.5-15	Not stipulate d	Yearly	No
United States	Yes	Blood & CGM	CGM	CGM	5.55-16.65	3 monthly	Yearly	No

Carter et al. reviews five newly diagnosed cases of type 1 diabetes in Israeli military aviators, who measured blood glucose half an hour before take-off and every 2 hours on long flights, but any out-of-range levels were not reported, nor was whether any remedial action was required.[7] Similarly, to our knowledge, there is only one published case report by Gray and Dupré of a Canadian Forces pilot with type I diabetes who continued on restricted flying duties. Other case reports from Canadian pilots have been reported as personal abstracts at aero-medical meetings but on each occasion no formal evaluation of blood glucose levels or rate of out-of-range values has been published.[8]

The first peer-reviewed paper reporting data from insulin-treated commercial pilots came from the United Kingdom by Mitchell et al in 2017.[9] This reported 4,900 flying hours from 16 pilots with insulin-treated diabetes awarded a Class 1 medical certificate by the UK Civil Aviation Authority as part of the ARA.MED.330 diabetes protocol.. The medical records were reviewed and data on demographic details, diabetes history and management were collated. All available HbA1c values pre- and post-certification were obtained, together with all in-flight blood glucose monitoring values.

Blood glucose monitoring data for these 16 pilots was collated between 2012 and 2015.[9] All were male, with a median age of 41 years, 22 (84.6%) had type 1 diabetes, with a median (range) duration of

diabetes of 7.75 (1-19) years. Before and after certification, HbA1c was unchanged (53.1 mmol/mol [95% CI 49.7-56.5] vs 54.8 mmol/mol [95% CI 50.9-58.8]), with a mean follow-up of 19.5 months. This result unequivocally showed that pilots did not run with higher blood glucose levels and overall diabetes control did not deteriorate with the attainment of a Class 1 medical certificate. The blood glucose measurement protocol was demonstrated to be both practical and feasible. Pilots had cumulative recordings of 8897 pre- and in-flight blood glucose values across 4,900 hours of flying. Only 186 readings were out of range: 181 were in the "caution" amber range (4.0-5.0 mmol/L or 15.0-20.0 mmol/L), with five in the "immediate action" red range (<4.0 mmol/L or >20.0 mmol/L). Appropriate action and retesting were undertaken by all pilots. There were no reported safety issues and the protocol was found to be feasible and practical.

A much more extensive follow-on study by Garden et al. was published in 2021 reporting over 22,000 flying hours with 49 pilots from the United Kingdom, Ireland and Austria (partners in the ARA.MED.330 protocol). This study represents the largest database from people treated with insulin undergoing a safety-critical occupation.[10] A total of 49 pilots issued Class 1 or Class 2 medical certificates for type 1 (84%) or type 2 (16%) diabetes were studied. The median diabetes duration was 10.9 years. The mean precertification HbA1c was 55.0 mmol/mol (7.2%) and the post-certification mean was 55.1 mmol/mol (7.2%; P = 0.97). A total of 38,621 blood glucose values were recorded during 22,078 flying hours. Overall, 97.69% of measurements were within the "green" range, 1.42% of values were within the low "amber" range, 0.75% were within the high 'amber' range, 0.12% were within the low "red" range and 0.02% were within the high 'red' range. An interesting observation was that out-of-range readings decreased from 5.7% in 2013 to 1.2% in 2019. This may be attributable to the widespread introduction of non-invasive CGM systems which many pilots were using in the later years in parallel to finger-prick glucose monitoring required by the protocol. No safety concerns have emerged using this established protocol, which has allowed pilots, of all classes, with insulin-treated diabetes to safely undertake complex safety-critical occupational duties.

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We will now take a closer look at the last study mentioned above, as it provides the most extensive data set for pilots with insulin-treated diabetes and is, therefore, highly relevant to our ongoing work on this project.

3. An evaluation of glucose metabolism and out-of-range readings in pilots with insulin-treated diabetes flying commercial and non-commercial aircraft within the ARA.MED.330 Diabetes Protocol May 2012-December 2019

Abstract

Aims:

The risk of hypoglycaemia in people with insulin-treated diabetes has debarred them from certain "safety critical" occupations, including flying commercial aircraft. The present report evaluates blood glucose measurements recorded as part of a diabetes protocol operated by the UK, Ireland and Austria which allows commercial airline pilots with insulin-treated diabetes to fly.

Research Design and Methods:

An observational study of pilots with insulin-treated diabetes granted medical certification to fly commercial and non-commercial aircraft. Clinical details as well as pre- and in-flight (hourly and within 30 minutes pre-landing) blood glucose values were correlated against a traffic light system: green 5.0-15.0 mmol/L (90-270 mg/dL); amber 4.0-4.9 mmol/L (72-89 mg/dL) and 15.1-20.0mmol/L (271-360 mg/dL); and red <4.0 mmol/L (<72 mg/dL) or >20.0 mmol/L (>360 mg/dL) and studied for trends in glucose concentrations, time course within flight and any consequences.

Results:

A total of 49 pilots with type 1 (n=41; 84%) or type 2 (n=8; 16%) diabetes who had been issued with class 1 or class 2 certificates were studied. Median diabetes duration was 10.9 years (IQR 7.3-14.9). Mean pre-certification HbA1c was 7.2±0.9% (55.0±9.7 mmol/mol) and mean post-certification 7.2±0.9% (55.1±9.6 mmol/mol), p=0.97. Forty-four pilots (90%) recorded one or more blood glucose value outside the green range during the seven years study period. Pilot age, diabetes type and duration, and follow-up period were comparable between subgroups and mean HbA1c did not differ before and after certification that would indicate poorer glycaemic control in any subgroup.

Blood glucose values (n=38,621) were recorded during 22,078 flying hours. Overall, 97.7% of measurements were within the satisfactory green range, 1.4% within the low amber range and 0.8% within the high amber range. Only 48 (0.1%) values were within the low red range, 14 (0.04%) of which occurred in-flight. All but four were restored to within the green range by the time of the next measurement. Six (0.02%) measurements were recorded within the high red range. Out of range readings declined from 5.7% in 2013 to 1.2% in 2019. Appropriate corrective action was taken for all out-of-range values with no reports of pilot incapacitation from any cause during any duty period.

Conclusions:

The protocol is practical to implement and no events compromising safety were reported. The traffic light system appears effective in identifying and reducing the frequency and severity of out-of-range values. The present study represents the most extensive data set for "safety critical" occupations for people with insulin-treated diabetes which may be relevant to estimate risk in other safety critical occupations.

3.1 Introduction

People with diabetes who require treatment with insulin have historically been precluded from safety-critical occupations, including flying commercial aircraft, because of the potential risk of hypoglycaemia which can cause unpredictable incapacitation.(1-3) Before the 1990s, it was widely accepted that insulin-treated diabetes signified an unacceptable aeromedical risk for pilots because hypoglycaemia of any severity could cause cognitive impairment and potential incapacitation. Additionally, the development of progressive microvascular and macrovascular diabetic complications, such as retinopathy or neuropathy, might also interfere with functional ability and flying performance.(3-5) However, advances in insulin pharmacokinetics, delivery systems and glucose monitoring technologies have greatly improved diabetes care over the past 30 years and have allowed these policies to be challenged and restrictions on flying reassessed.

While several countries grant aeromedical certification for leisure purposes (1, 4, 5), it was not until 2002 when the first carefully selected pilots with insulin-treated diabetes were permitted to fly commercial aircraft by the Canadian Aviation Authority.(6) Current EU regulation does not permit the issuance of class 1 medical certificates (required to validate a commercial pilot's licence) or class 2 medical certificates (required to validate a private pilot's licence) to people with insulin-treated diabetes. However, a mechanism exists within the regulation for circumstances whereby the identification of new medical technologies, medications or procedures may justify the assessment of applicants as to whether they are fit to fly. Through this mechanism, the UK Civil Aviation Authority (UK CAA) convened an expert committee in 2010 to review scientific knowledge and subsequently developed a protocol for medical assessment and evaluation, with appropriate limitations, to ensure safe flying by insulin-treated pilots.(7) The protocol was rolled out in 2012 and the UK CAA began issuing class 1 medical certificates to a defined number of insulin-treated commercial pilots. In 2014, a joint protocol by the UK and Ireland was developed and notified to the European Union Aviation Safety Agency (EASA) as a research protocol. In 2016 Austria also joined the protocol and EASA was informed accordingly.

At the time the protocol was initiated there was not sufficient data on the safety and accuracy of continuous glucose monitoring (CGM) and therefore pilots are required to measure capillary blood glucose obtained by finger-prick. Blood glucose measurements are measured before and during each flight and pilots use a traffic light system of ranges to determine any further action necessary. The protocol demands clinical oversight, documentation, and systematic collection of data. However, some commentators expressed concerns about the practicality of performing in-flight glucose measurements and speculated that the avoidance of low glucose values in the protocol would lead to suboptimal glycaemic control and increase the risk of diabetic complications.(2, 8)

The results from the UK pilots who were certificated from 2012 until March 2015 were published in 2017.(9) A further study collated data from 49 pilots from the UK, Ireland and Austria who had been using the protocol between its introduction in 2012 and December 2019. It represents the only systematic collection of data from a safety-critical occupation that allows operatives treated with insulin. Pre- and in-flight blood glucose monitoring data, collected since 2012, were evaluated.

The evaluation includes in depth analysis of all recorded blood glucose measurements that were outside of the satisfactory range in the traffic light system to ascertain preceding and subsequent glucose concentrations, their time course during flight, and any consequences to be confident that the amber and red action ranges were appropriate to prevent any form of incapacity. In addition, the characteristics of pilots recording out of range results were examined.

3.2 Research Design and Methods

Pilots with insulin-treated diabetes holding a class 1 or a class 2 medical certificate must perform a series of capillary blood glucose measurements, obtained by finger-prick, using an ISO 9000 certified meter. Pre-flight glucose measurements one hour before reporting for duty or two hours before commencing a flight are mandatory and must be repeated within 30 minutes before take-off to confirm that blood glucose is stable and within range. Once airborne, measurements must be performed every hour for the duration of the flight and within the 30 minutes before landing, with additional glucose testing if a pilot experiences symptoms that suggest a high or low blood glucose concentration.

A traffic-light system for blood glucose interpretation was devised to govern acceptable pre and in-flight glucose ranges and provide direction for appropriate corrective action where necessary (see appendix 1).(7, 9) Glucose values between 5.0-15.0 mmol/L (90-270 mg/dL) are considered to be satisfactory and are coded green with no action being required. Values between 4.0-4.9 mmol/L (72-89 mg/dL) and 15.1-20.0 mmol/L (271-360 mg/dL) are coded amber to indicate caution and the potential need for intervention. A glucose of <4.0 mmol/L (<72 mg/dL) or >20.0 mmol/L (>360 mg/dL) is coded red and requires immediate action. Low amber values require the pilot to ingest 10-15g of readily absorbed, fast-acting carbohydrate and re-measure blood glucose after 30 minutes. Low red values require the pilot to demit flying duties to the co-pilot or, if flying solo, consider landing as soon as is practical, as well as ingesting 10-15g of readily absorbed carbohydrate and retesting blood glucose after 15 minutes. High readings >15.0 mmol/L (>270 mg/dL) necessitate a review of insulin dosing, modification of planned carbohydrate intake, or both. A high red reading also requires the pilot to demit flying duties to the co-pilot and, if flying solo, consider landing as soon as is practical. A pilot flying with other crew must wait for 45 minutes after the blood glucose has returned to within the green range following a low or high red range reading before resuming duties.

The protocol stipulates that all commercial pilots must brief their co-pilot about the testing regimen and the action required for out-of-range values before each flight. Every blood glucose measurement must be cross-checked with the co-pilot and read aloud to be captured by the cockpit voice recorder. The glucose readings and any action taken for out-of-range values must also be recorded in the pilot's flying hours logbook for compliance monitoring.

The pilots must attend a clinical review with an independent CAA Diabetes Specialist every six-monthly for commercial pilots, or annually for private pilots, to monitor their diabetes management and their compliance with the protocol. During each assessment, the glucose test meter is reviewed against the pilot's logbook entries to ensure protocol compliance. Glycaemic control is evaluated using glycated haemoglobin (HbA1c) which is measured every six months, along with plasma lipids, urea, and creatinine. An assessment of hypoglycaemia awareness is undertaken using the Gold score (10) and a recording of glucose level at which symptoms develop is made. A systems examination is performed, including assessment for neuropathy using a 10g monofilament, blood pressure and weight, and the results of annual retinal screening and annual cardiovascular review are documented.

Every pre- and in-flight capillary blood glucose measurement recorded by the individual pilots was entered into their logbooks. All values obtained since the protocol commenced were transferred to an Excel spreadsheet with each pilot's consent. Qualitative data and statistical analysis were performed using Microsoft Excel 2010 and IBS SPSS statistics software version 25 (IBM). Data are expressed either as mean and standard deviation or median and interquartile range, as indicated. Statistical significance is demonstrated using the t-test.

For this study the term duty period described the pre-flight window commencing one hour before a pilot reported for duty, or the two hours before take-off and the full duration of the flight until the aircraft has landed, for both commercial and private pilots.

3.3 Results

Pilot Demographics

Between May 2012 and December 2019, 49 pilots with insulin-treated diabetes (84% type 1, 16% type 2 diabetes) participated in the study. Of these pilots, 30 (61%) had been issued with class 1 medical certificates and 19 (39%) with class 2 medical certificates. Demographic details are shown in Table 1. Most were male (96%) with a median age of 44 years (IQR 34-56) and median diabetes duration of 10.9 years (IQR 7.3-14.9). The mean duration of follow-up after issue of their certificate was 4.3 ± 2.3 years. The mean pre-certification HbA1c was 7.2 ± 0.9% (55.0 ± 9.7 mmol/mol) and final follow-up mean HbA1c was 7.2 ± 0.9% (55.1 ± 9.6 mmol/mol). A paired t-test comparison between the mean pre- and post-certification HbA1c found that no significant change in glycaemic control had occurred (p=0.96).

Since the protocol was introduced no neuropathy, determined by 10-gram monofilament perception at each six-monthly medical review, or evidence of nephropathy, as measured by estimated glomerular filtration rate >60 ml/min/1.73m^2 and absence of clinical evidence of microalbuminuria, has been reported. All pilots had normal visual acuity. Seventeen pilots had evidence of diabetic retinopathy at baseline or at the time of one or more annual retinal screening reviews during the study period. In five patients the background retinopathy had resolved by their next annual retinal review while in 12 pilots the retinopathy had persisted but without progression. One pilot, prior to certification, had required photocoagulation for maculopathy in both eyes in 2012 and 2013 but still met the visual acuity standard required for flying.

Forty-four (90%) of the 49 pilots recorded one or more blood glucose values outside the green range (5.0-15.0 mmol/L; 90-270 mg/dL) while on duty during the seven and a half years of the study. Fifteen pilots (31%) recorded values in the low red range (<4.0 mmol/L; <72 mg/dL), 39 pilots (80%) reported low amber range values (4.0-4.9 mmol/L; 72-89 mg/dL), 29 pilots (59%) recorded high amber range values (15.1-20.0 mmol/L; 271-360 mg/dL) and three pilots (6%) recorded one or more high red range reading (>20.0 mmol/L; >360 mg/dL). All pilots who recorded low red values also reported low amber range values and the three pilots who recorded high red readings also documented high amber range values. Nearly half of all pilots (49%) documented both high and low out of range values. Only five pilots recorded no values outside of the desired green range.

Demographic data for all pilots reporting out-of-range measurements within each out-of-range subcategory are shown in Table 2. Across all four out-of-range subcategories most of the pilots had type 1 diabetes and held a class 1 medical certificate. No pilots with type 2 diabetes recorded a value >20.0 mmol/L (>360 mg/dL). The subgroup of pilots recording low red values had the highest percentage (87%) of pilots holding a class 1 medical certificate and the highest median age of 53 years (IQR 46-57 years). Diabetes duration and duration of follow-up were comparable between all four out-of-range subgroups. No statistical difference was found in mean HbA1c before certification and after an average of 4.3 ± 2.3 years of follow-up in any of the subgroups suggesting that no change in the quality of glycaemic control had occurred to account for the abnormal glucose values.

The five pilots who recorded all blood glucose values in the green range were older with a median age of 55 years (IQR 52-58 years), had a significantly shorter duration of diabetes of only 7.5 years (IQR 7-14.9 years), and a shorter period of follow-up at 3.6 years (IQR 1.6-3.7 years).

Glucose Concentration and Out-of-Range Values

A total of 38,621 capillary blood glucose measurements were recorded within the duty period. The results of all pre- and in-flight blood glucose measurements for all pilots are shown in Table 3 and Figure 1. Overall, 37,729 (97.7%) of all measurements were within the satisfactory green range. Only 892 (2.3%) values were outside of the green range. Most out-of-range values recorded were within the caution amber range (n=838; 2.2% of all readings), of which 550 (1.4%) were low amber and 288 (0.8%) were high amber. Fifty-four (0.1%) measurements were within the immediate action red range with 48 (0.1%) of these readings within the low (hypoglycaemia) red range and six (0.02%) within the high

(hyperglycaemia) red range.
Sub-analysis of the 48 low red readings showed that 34 were recorded within the pre-flight period representing 0.2% of pre-flight measurements and 0.1% of all capillary blood glucose values recorded. Twenty-five of these were recorded by ten pilots with class I certificates and represent 0.2% of class 1 pre-flight capillary blood glucose measurements. The remaining nine low red values were recorded by two pilots awarded class 2 medical certificates, representing 0.6% of class 2 pre-flight capillary blood glucose measurements.

Fourteen of the forty-eight low red values were recorded in-flight representing 0.07% of in-flight measurements and 0.04% of all capillary blood glucose values analysed. All but one of these values were recorded by eight commercial aircraft pilots (awarded class 1 certificates). One was recorded by a pilot with a class 2 certificate. These 14 values represent 0.07% of all in-flight low red measurements for each class. This equates to a blood glucose value of <4.0 mmol/L (<72 mg/dL) occurring during 0.2% of commercial flights over the study period. Five pilots recorded only one low red reading, two pilots each had two low red readings and one pilot reported four values <4.0 mmol/L (<72 mg/dL). This individual accrued 3,161 flying hours over 1,126 separate flights, significantly more flying hours of any other pilot over the study period. The 14 low red in-flight values were recorded at various stages of flight on 14 separate flights. These are represented as a red asterix in Figure 1. The lowest capillary blood glucose recorded in-flight was 3.1 mmol/L (56 mg/dL) and all the recorded episodes <4.0 mmol/L (<72 mg/dL) were self-treated. There were no episodes of severe hypoglycaemia (requiring help for recovery).

Sub-analysis of the six high red measurements showed that all six values were recorded by three individual pilots all of whom had type 1 diabetes. Four had been recorded pre-flight, representing 0.02% of pre-flight measurements and 0.01% of all capillary blood glucose measurements. Three of these values were recorded by a single pilot holding a class 1 certificate and one was recorded by a class 2 certificate pilot. Two of the six high red values were recorded in-flight, one by a pilot issued a class 1 certificate and one by a pilot issued a class 2 certificate (0.01% of all blood glucose values recorded). Both in-flight high red measurements were recorded within the 30 minutes before the aircraft landed. The highest recorded in-flight value was 21.1 mmol/L (380 mg/dL).

Appropriate action was taken by the pilots for out-of-range measurements. In particular, rapidly absorbed carbohydrate was ingested to correct low readings and no adverse events were reported. None of the pilots within the study were incapacitated for any reason during any flight. In 2014 there was one aircraft accident involving a 50 year old pilot with insulin treated diabetes. The pilot was following the ARA.MED.330 protocol but has not been included within this retrospective study as participant consent to share data was sought in 2015, after the pilot`s death. More details of this accident are discussed later in this report.

Glucose Variability Over Flight Time
Over the seven and a half years of the study, data from 9,189 flights accruing 22,078 flight hours were obtained. Of these, 8,036 flights (range 3 to 1,126) (87.5%) and 20,848 hours (range 13 to 3,161) (94.4%) had been performed by pilots with a class 1 medical certificate. Pilots issued a class 2 medical certificate had undertaken 1,230 hours (range 3 to 293) (5.6%) over 1,153 flights (range 3 to 541) (12.5%).

Table 4 displays all pre-flight and in-flight values recorded outside of the satisfactory green range and when they were recorded in relation to flight time. Of the 892 out-of-range values documented, 50.2% were recorded within the pre-flight period, half of which (24.9%) occurred in the final 30 minutes before take-off. Figure 2 (Panels A–C) shows the serial measurements of blood glucose concentrations in individual pilots after an out-of-range value had been recorded within the final 30 minutes before take-off. Thirty-four (70.8%) of the 48 low red range values were recorded pre-flight, of which ten (30%) were reported within the final 30 minutes before take-off. The lowest blood glucose concentration recorded during a duty period was 3.0 mmol/L (54 mg/dL). This occurred within the two hours before commencing flight; with corrective measures, blood glucose increased to 8.8 mmol/L (158 mg/dL) before take-off. All

pre-flight low red values were corrected to within the acceptable green range before take-off except for one which was corrected into the amber range.

The 49.8% of out-of-range readings that were recorded in-flight, occurred at various times during flight. One third (33.3%) were reported during the first hour of the flight with a further third (31.5%) recorded in the final 30 minutes of the flight (pre-landing). The flight duration was analysed for all 9,189 flights. Just over half (51.8%) of the out-of-range values recorded in-flight occurred during short-haul flights of three hours or less and during private flying (3.0% of all short-haul flights); 31.8% were reported during medium-haul flights (3-6 hours) (15.0% of all medium-haul flights); and 16.4% were documented during long-haul flights over six hours duration (13.9% of all long-haul flights). Only 14 in-flight values were recorded within the low red range across the 9,189 flights. All were recorded within the first six hours of the flight (71.4%) or within 30 minutes before landing (28.6%). Four were reported on short-haul flights, six on medium-haul flights and four on long-haul flights. The lowest in-flight blood glucose concentration of 3.1 mmol/L (56 mg/dL) was recorded within an hour of take-off. Figure 3 (Panels A–C) displays the trends in blood glucose concentration before, and after out-of-range values had been recorded in-flight.

Scrutiny of the 48 glucose values in the hypoglycaemic range ascertained that, despite a total of 550 low amber readings being documented, only three of the low red range values had directly followed a low amber value. Twenty-four were the first value recorded in the duty period. The remaining 21 all followed measurements within the green range. All but nine of the 48 low red values were corrected satisfactorily to within the green range by the time of the next measurement fifteen minutes later. Five were within the caution amber range before restoration to within the green range and four were recorded within the 30 minutes prior to landing so after carbohydrate was ingested no subsequent blood glucose readings were recorded during the same duty period.

On only six occasions was a blood glucose value in the high red hyperglycaemic range recorded throughout the entire study period. Four occurred within the pre-flight period, two of which were recorded within 30 minutes before take-off. The two in-flight high red readings were both recorded within the 30 minutes before landing, one on a short-haul flight and the other on a medium-haul flight. One the six high red values was within the satisfactory green range by the time the subsequent reading was taken, two readings were during the same pre-flight duty and the pilot's blood glucose had returned to the green range before the first in-flight recording, and two were within 30 minutes prior to landing the aircraft. One pre-flight high red in a class 2 certificate pilot was caused by inadvertently consuming a drink containing a high sugar content.

Rates of Change in Glycaemic Concentration

Data were analysed for each year of the study with all out-of-range measurements shown in Figure 5. The frequency of out-of-range readings decreased from 5.7% in 2013 to 1.2% in 2019. The greatest annual decline observed was in the percentage of low amber readings, which fell from 5.0% in 2013 to 0.7% in 2019. High amber values, which initially were 0.3% in 2013, increased to 1.1% in 2014 before falling thereafter to 0.5% in 2019. Low red range readings were unchanged (0.2% in 2013 and 0.1% in 2019) and high red range values were completely absent by 2017. After 2016, no capillary blood glucose measurements above 20.0 mmol/L (360 mg/dL) were recorded by pilots and any point during the duty period.

Change In Out-of-Range Values Over the Study Duration

Data were analysed for each year of the study with all out-of-range measurements shown in Figure 5. The frequency of out-of-range readings decreased from 5.7% in 2013 to 1.2% in 2019. The greatest annual decline observed was in the percentage of low amber readings, which fell from 5.0% in 2013 to 0.7% in 2019. High amber values, which initially were 0.3% in 2013, increased to 1.1% in 2014 before falling thereafter to 0.5% in 2019. Low red range readings were unchanged (0.2% in 2013 and 0.1% in 2019) and high red range values were completely absent by 2017. After 2016, no capillary blood glucose

measurements above 20.0 mmol/L (360 mg/dL) were recorded by pilots and any point during the duty period.

3.4 Discussion

Flight Safety and Hypoglycaemia

To ensure the highest safety standards, the aviation industry has developed a multitude of safety measures, which includes repeated assessment of a pilot's medical fitness to confirm functional ability and estimate incapacity risk. Some medical disorders prohibit pilots from obtaining a medical certificate to validate a pilot's licence and until recently this included insulin-treated diabetes. The main risk is the potential for developing hypoglycaemia, although hyperglycaemia has also been proven to interfere with cognition and reaction times. Hypoglycaemia is the most common side effect of insulin therapy and the principal barrier to achieving optimal glycaemic control.(11, 12) The American Diabetes Association and European Association for the Study of Diabetes position statement defines hypoglycaemia as a plasma glucose of less than 3.0 mmol/L (<54 mg/dL, level 2) while 3.9 mmol/L (70 mg/dL, level 1) is designated as an alert level at which patients should take avoiding action to prevent progression to clinically significant hypoglycaemia.(13) Severe hypoglycaemia (level 3) is defined by the inability to self-treat and is characterised by the development of neuroglycopenia, which causes impairment of cognitive function with complex and speed-dependent tasks being affected most.(14) While a blood glucose at or below 3.0 mmol/L (54 mg/dL) would be very likely to have an adverse effect on flying skills and performance, some degree of cognitive impairment could commence above this level. As a result, the European ARA.MED.330 diabetes protocol determined a glycaemic concentration of 4.0 mmol/L (72 mg/dL) as the threshold level for intervention. Although most studies have focused on hypoglycaemia, high blood glucose can also be associated with impaired reaction time.(14-17) Any impairment in decision-making and the ability to perform tasks with speed and precision would have an adverse effect on a pilot's flying performance, which could have very serious consequences. The purpose of the traffic light system utilised in the protocol is to alert pilots as to when to take corrective action to avoid any risk of developing cognitive impairment and mood change resulting both from unduly low and high blood glucose concentrations.

Hypoglycaemia within the ARA.MED 330 Protocol

The present study represents the largest systematic collection of blood glucose data in a cohort of people with insulin-treated diabetes undertaking an important safety-critical occupation. No episodes of incapacitation or any safety problems were reported during duty hours over the seven and a half years of the study by the participating pilots.

The pilot with insulin-treated diabetes who died in the aircraft accident in 2014 was flying under the ARA.MED.330 diabetes protocol and managing his diabetes in accordance with the protocol. While pilot incapacitation due to hypoglycaemia was excluded as the cause of the accident the post-mortem examination did not reveal anything that could have contributed to the accident.

The ARA.MED.330 protocol was shown to be feasible, practical, and easily understood by co-pilots. Very few blood glucose values (2.3%) were recorded outside of the satisfactory range coded green in the traffic light system, with the lowest in-flight blood glucose measurement being 3.1 mmol/L (56 mg/dL) and the highest 21.1mmol/L (380 mg/dL). Scrutiny of the data found appropriate action had been taken by the pilots for all out-of-range measurements and blood glucose levels were corrected into the safety zone.

During the study only 48 (0.1%) of 38,621 blood glucose values recorded, were within the low red, hypoglycaemic range and 550 (1.4%) were within the low amber range. Analysis of the low red measurements showed that only three of the 48 values directly followed a low amber value. All but four of the 48 low red values were corrected to a glucose concentration within the desired green range by the time of the next glucose measurement. The four other values had increased to within the low amber

range before being restored to the safety of the green range. This supports the view that traffic light graduation, which requires action to be taken for amber (non-critical) blood glucose levels, is highly effective and contributed to the very low number of potential safety-critical values that were recorded. Furthermore, over two-thirds of the low red values occurred in the pre-flight period and following corrective action all except one had returned to within the desired green range before the flight. This step in the protocol that requires two pre-flight measurements to be performed, allows sufficient time for pilots to take corrective action to ensure that their blood glucose is within the acceptable green range before take-off. Because the pre-flight screening process was effective, no pilot had to be excluded from duty.

A further observation was that the rates of decline and recovery of blood glucose following out-of-range readings were greater with red than with amber values. While this may reflect a greater urgency of the pilot to correct an abnormal reading, this does not explain the steeper rate of glycaemic descent observed with low red readings.

Impaired Hypoglycaemia Awareness

The certification of pilots with insulin-treated diabetes is enabled by a research protocol developed by UK and Ireland in accordance with the provisions of ARA.MED.330 of the EU Aircrew Regulation. The protocol was notified to EASA and permits insulin-treated pilots to fly, providing they meet certain criteria. As well as demonstrating strict glycaemic control and normal parameters of micro and macrovascular complications, pilots must have intact hypoglycaemia awareness. Hypoglycaemia awareness is assessed at each pilot's six-monthly (commercial pilot) or annual (private pilot) medical review using the Gold Score.(10) Impaired hypoglycaemia awareness is characterised by a diminished ability to detect the onset of hypoglycaemia with evidence of the loss or delayed onset of autonomic warning symptoms, thereby increasing the risk of neuroglycopenia and progression to severe hypoglycaemia.(18) It affects 20-25% of people with type 1 diabetes (10, 18, 19) and up to 10% with insulin-treated type 2 diabetes (20, 21) and can also be associated with strict glycaemic control.(19) Impaired hypoglycaemia awareness increases the risk of severe hypoglycaemia (level 3) six-fold in people with type 1 diabetes (10, 19) and up to 17-fold in people with type 2 diabetes requiring insulin.(20) There were no reports of impaired awareness of hypoglycaemia in any of the pilot within this study, and external assistance was not required to treat any episodes of hypoglycaemia.

Long-term Glycaemic Control

There were concerns that pilots might allow a higher blood glucose range in order to avoid any risk of hypoglycaemia.(2, 8) The results of this study do not support such a premise. Diabetes control for all pilots, as measured by HbA1c, did not deteriorate over the period of the study with a mean follow up period of 4.3 years from certification. Demographic details of pilots across all subgroups reporting out of range readings were also similar. Mean HbA1c ranged from 54.4 mmol/mol to 57.1 mmol/mol (7.1% to 7.4%) pre-certification and from 55.2 mmol/mol to 58.0 mmol/mol (7.2% to 7.5%) post-certification, indicating that no significant difference in glycaemic control had occurred in the pilots in each of the sub-groups. As a group, pilots are highly trained, well-motivated and generally manage their diabetes with considerable care. They are accustomed to frequent monitoring of instruments during flight and had no problem accommodating additional glucose monitoring. In the present study they were able to successfully balance close adherence to the protocol with the maintenance of excellent long-term glycaemic control.

Another facet of the protocol that should be noted is the ongoing surveillance for microvascular and cardiovascular complications, which could also interfere with flying performance. Clinical surveillance has not identified the development of any new clinically significant micro- or macrovascular diabetes-related complications within the limited period of the study.

3.5 Validity of Data

Although the study depended on accuracy of reporting by individual pilots, all in-flight blood glucose values recorded were verified by the co-pilot, who would not usually be known to the first pilot, and spoken into the flight voice recorder. Both pre- and in-flight values documented in the pilot's logbooks were verified against their blood glucose meter readings at the medical reviews by an independent medical examiner to ensure accuracy of the recorded data. A copy of the logbook and a download from the glucose meter are retained in the pilot's aviation medical notes.

Continuous Glucose Monitoring

When the current protocol was devised in the UK in 2010, it was determined that non-invasive continuous glucose monitoring (CGM) did not provide sufficient accuracy and could not be relied upon to meet safety standards. However, subsequent trials of modern real-time CGM devices have demonstrated that their usage leads to an increase in the time in range, a reduction in the number and severity of hypoglycaemia episodes, and a reduction in time spent both in hypo- and hyperglycaemia.(6, 22-26) This technology has been suggested as being applicable for use by pilots on the flight deck. Many of the pilots in this study began using CGM devices in addition to testing finger stick blood samples, as stipulated by the protocol, during duty periods. The widespread introduction and availability of non-invasive flash glucose monitoring and CGM systems has likely contributed to the considerable decline observed in the number of out-of-range values and the reduction in variability of glucose levels over the seven and half year study duration. Additionally, further education, enhanced insulin replacement regimens leading to improved self-care, and an increase in pilot experience using the inflight glucose monitoring schedule may also have played a role.

Employing such a device in the cockpit provides the pilot with access to instant glucose values and glucose trends, which guide treatment decisions and enable them to make subtle insulin adjustments to avoid undesirable high and low glucose concentrations.(22) Some systems forecast rapidly rising or falling glycaemic trends and enable the pilot to take corrective action while their glucose concentration is still within the satisfactory green range. The use of CGM technology has yet to be proven within the hypobaric environment of an aircraft cockpit but a feasibility study on a small number of pilots was promising.(27) If the efficacy of CGM use within the cockpit is determined it could play a fundamental role in demonstrating that continuous monitoring enhances aviation safety in regard to pilots with insulin treated diabetes allowing at the same time for more flexibility regarding the aero-medical certification of pilots and ATCOs. The United States Federal Aviation Authority (FAA) acknowledged the value of CGM in this context and since the end of 2019 the USA has allowed insulin-treated pilots to fly commercial aircraft.(28) Moreover, incorporating recent guidance concerning recommended glucose ranges obtained from CGM and including new internationally-agreed definitions of hypoglycaemia, could lead to modifications of the current protocol which is based on glucose monitoring using meters.(29)

3.6 Conclusion

Only a small number of states have ITDM certification criteria for pilots and ATCOs (see our next deliverable, tasks 4/5). There is a real scarecity of inflight and monitoring data. The present study, however, represents systematic collection of the most extensive data set for safety critical occupations for people with diabetes treated with insulin on which future protocols may be based. It exhibits a detailed examination of all out-of-range blood glucose levels that were recorded by pilots with insulin-treated diabetes before and during flight, within the operational protocol. The glucose profiles and actions following out-of-range results suggests the current protocol is relatively fit for purpose and supports its continued application for insulin-treated pilots. In particular, the traffic light rules that demand action at non-safety-critical levels appears to prevent and reduce the frequency of significantly out-of-range values.

The protocol that is currently being used by the UK, Ireland and Austria is practical and feasible to operate. It allows insulin-treated pilots to fly commercial and private aircraft safely and to function consistently in the safety-critical environment of the cockpit. This protocol and concept may be applicable to other safety-critical environments from which people with insulin-treated diabetes have historically been precluded because of the perceived risk of hypoglycaemia or hyperglycaemia.

3.7 Significant events: All of these occurred in people not participating in the observation trial or occurred after the end of the observation period which took place between 1st May 2012-31st December 2019.

A total of five adverse events have occurred since the protocol was rolled out in 2012. Two events took place during flight whilst pilots were using the ARA.MED.330 protocol. One event occurred whilst in-flight when the pilot was the safety pilot but was not following the protocol and two events occurred during free living, outside of the protocol.

3.7.1 Accident A

Pilot A was a 50 year old commercial pilot with a class one certificate. He had type 1 diabetes and was treated with insulin.

Incident
In 2014, the aircraft was carrying out a local flight with the pilot and a passenger on board. The aircraft was observed flying at low level five minutes into the flight. After carrying out a level turn, the aircraft climbed sharply and entered a stall or spin which did not recover from before striking the ground. Both occupants were fatally injured in the impact.

Assessment and outcomes
Upon conducting their investigation of the incident, the UK Air Accidents Investigation Branch reported the following:

Toxicology
A specialist aviation pathologist carried out post-mortem examinations of the pilot and passenger. He noted that both 'died of multiple injuries which were sustained in the non-survivable crash of their aircraft'. Toxicological investigation revealed nothing that could have contributed to the accident.
Toxicological evidence (usually from a sample of the vitreous of the eye) indicated that the pilot was not hypoglycaemic at the time of the accident and there was nothing to suggest that his diabetes had played any role in the accident.

Conclusion
The pilot was an experienced aviator and suitably qualified. He was diabetic and managed his condition in accordance with the CAA's protocols. He held a Class One medical certificate and the post-mortem examination revealed nothing that could have contributed to the accident.

The low height at which the aircraft was flying when first noticed by eyewitnesses may indicate that the flight was not proceeding normally. It is possible that a problem led to the pilot choosing to descend to low height. There was evidence that the engine was running at the moment the aircraft struck the ground but the possibility of a significant loss of engine power could not be discounted.

No defects were found in those parts of the flying controls that remained but the engineering investigation was hampered by the fact that some components were damaged or destroyed in the post-crash fire.

The aircraft's final manoeuvre could not be explained but, having entered a stall or spin, there was little height in which the pilot could regain control before it struck the ground.

3.7.2 Accident B

Pilot B is a 22 year old with class 2 certification, recorded to have flown 13 hours in a PA28 since his last review. He was diagnosed with type 1 diabetes at the age of 4 and was managed with Novorapid insulin via an insulin pump (Medtronic 640G with auto-suspend). His daily regimen is 20 units of basal insulin with 1 unit per 9g of carbohydrate. His most recent HbA1c has increased a little to 64 mmol/mol (8.0%).

Incident
At take-off, blood glucoses were 9.8 and 12.8 but 20 minutes into the flight he felt slightly hypoglycaemic. He took sweets and recorded a glucose of 3.7 mmol/L. As he was flying solo and within easy reach of his airfield, he returned and landed without incident.

Assessment and outcome
On review, he has not required any third-party assistance in the past 5 years. He records blood glucose frequently and is aware of when it falls below 4 mmol/L. His Gold score was 2 and glucose records show some variability which has responded to the use of CGMS and auto-suspend. He has had no significant hypoglycaemic episodes in the past year. The recommendation was that a 3-month blood glucose records that demonstrate reduced variability before being allowed to fly again.

3.7.3 Accident C

Pilot C was a 43 year old commercial pilot with a class 1 medical certificate. He had type 1 diabetes and was treated with insulin.

Incident
Pilot C was on-board a commercial flight as the safety pilot accompanying two pilots who were in control of the aircraft. As the safety pilot he was present in the cockpit throughout the flight. The wording of the protocol at the time led to some ambiguity and the pilot believed it was not necessary follow the protocol as he was not piloting the plane. Consequently, he was not recording or documenting his blood glucose. During his meal, he had a pasta-free lasagne and administered his usual dose of insulin without knowing its reduced carbohydrate content. After the flight had landed, pilot C entered a hypoglycaemic state in the cockpit and required third-party assistance.

Assessment and outcome
The incident could be explained by inappropriate insulin for a non-pasta containing lasagna. The fact that he understood that he was not formally requiring to measure and record his blood glucose also contributed to the event. It was recommended that the protocol should be amended to clarify that all personnel on the flight deck within insulin-treated diabetes must adhere to the protocol and in addition the pilot was required to submit blood glucose monitoring data from free living for review prior to being deemed fit to fly again.

3.7.4 Accident D

Pilot D is a 57 year old with class 1 certification, recorded to have flown 40 hours in A320 jets since his last review. He was diagnosed with type 1 diabetes in 2015 and was controlled with twice daily Levemir insulin (21 and 11 units) and 1 unit of Novorapid insulin per 10g of carbohydrate. Additionally, he has a background of coeliac disease that is stable on a gluten-free diet. He also takes Candesartan and Simvastatin regularly. His most recent HbA1c was 57 mmol/mol (7.4%) with glycaemic control of 73% time-in-range and 3% below.

Incident
He experienced a disabling hypoglycaemic episode at 12:15 (lunch time) on 23/04/2023. That morning he woke at 7am and had little sleep the evening prior. After eating a normal breakfast and taking the usual insulin, his glucose were running high so he took an additional insulin correction dose. He was preparing lunch when his Dexcom CGM stated his glucose was falling and while awaiting lunch, he had a disabling hypoglycaemic episode. This was accompanied by a witnessed seizure, with tongue biting noted. Glucogel was administered when emergency response team attended and subsequent investigations of CT head scan and ECG found no abnormality.

Assessment and outcome
On review of his Dexcom data, he has had remarkably few low values prior to the event and never required third-party assistance previously. His Gold score has always been recorded as 1. His injection sites were noted to be lumpy and may have contributed to the event alongside the lack of sleep and delayed food intake. The recommendation was that he should not fly until he is stabilised on a new insulin regimen (awaiting review) and demonstrates adequate hypoglycaemic awareness.

3.7.5 Accident E

Pilot E is a 72 year old flying instructor with type 3c diabetes secondary to acute pancreatitis. He was managed using insulin and Freestyle Libre. He had an episode in March 2017 with severe hypoglycaemia that required third-party assistance and hospital admission. He has not had further severe hypoglycaemia episodes since then and was able to maintain a tight glycaemic control. His most recent HbA1c was 51 mmol/mol (6.8%).

Incident, assessment, and outcome
On review, his recent profiles show that he tends to run low and that this episode was precipitated by a glass of wine which caused his glucose level to fall lower than usual. His glycaemic control was not satisfactory and decisions was for further glucose data review in another 3-4 months.

3.8 Conclusions

To date, there have been no in-flight incapacitations or serious incidence that have been proven to be directly caused by diabetes. Diabetes events have been recorded when the protocol was in operation. The cause of the aircraft accident that lead to the death of pilot 1 and the passenger could not be determined. While hypoglycaemia was excluded, other sudden or subtle incapacitation could not be excluded and therefore remain a potential cause of the accident. Many other potential causes unrelated to diabetes were also not excluded. The protocol should be in operation for all those on the flight deck and the protocol has been amended to reflect this following the incident involving pilot 3. The event involving pilot 2 demonstrates that the protocol works well in identifying out of range CBG values early and provides a course of action for pilots to follow should they record a blood glucose values outside of the satisfactory green range.

Overall:

- The experience demonstrates that with strict adherence to the ARA.MED.330 diabetes protocol pilots with insulin treated diabetes are able to perform their safety critical duties with additional mitigating measures.
- The regular monitoring of blood glucose as stipulated in the protocol is essential to ensure safety.
- A traffic light system requiring action when thresholds are crossed appears to work well.
- Advances in monitoring glucose techniques has contributed to the lower rates of out-of-range readings in the ARA.MED.330 protocol over time.

- The improvements in diabetes treatments, including new insulin preparations, has contributed to the lower rates of out-of-range readings within the ARA.MED.330 protocol over time.

Tables

Table 1: Pilot demographics including age, gender, pilot certificate class, type of diabetes, duration of diabetes, pre-certification HbA1c, most recent post-certificate HbA1c and presence of retinopathy.

Age	**Years (median; IQR)**	**44 (34-56)**
Gender	Male (%)	47 (96)
	Female (%)	2 (4)
Pilot certificate class	Class 1 (%)	30 (61)
	Class 2 (%)	19 (39)
Type of diabetes	Type 1 (%)	41 (84)
	Type 2 (%)	8 (16)
Duration of diabetes	Years (median; IQR)	10.9 (7.3-14.9)
Pre-certificate HbA1c	Mean HbA1c mmol/mol ± SD (% ± SD)	55.0 ± 9.7 (7.2 ± 0.9)
Most recent HbA1c (4.3 years post-certification)	Mean HbA1c mmol/mol ± SD (% ± SD)	55.1 ± 9.6 (7.2 ± 0.9)
Presence of retinopathy	No retinopathy (%)	36 (73)
	Background retinopathy (%)	12 (25)
	Retinopathy/maculopathy (%)	1 (2)

Table 2: Pilot demographics for all 49 pilots analysed in each blood glucose range subgroup

	Low Red (<4.0 mmol/L: <72 mg/dL), n = 15†	Low Amber (4.0-4.9 mmol/L: 72-89 mg/dL), n = 39‡	All Green (5.0-15.0 mmol/L: 90-270 mg/dL), n = 5§	High Amber (15.1-20.0 mmol/L: 271-360 mg/dL), n = 29¶	High Red (>20.0 mmol/L: >360 mg/dL), n = 3††	All Pilots n = 49
Age, median years (IQR)	53 (46-57)	42 (34-54)	55 (52-58)	44 (34-56)	44 (37-44)	44 (34-56)
Sex						
Male, n (%)	15 (100)	38 (97)	4 (80)	29 (100)	3 (100)	47 (96)
Female, n (%)	0	1 (3)	1 (20)	0	0	2 (4)
Medical certificate						
Class 1, n (%)	13 (87)	27 (69)	1 (20)	19 (66)	2 (67)	30 (61)
Class 2, n (%)	2 (13)	12 (31)	4 (80)	10 (34)	1 (33)	19 (39)
Type of diabetes						
1, n (%)	13 (87)	33 (85)	3 (60)	26 (90)	3 (100)	41 (84)
2, n (%)	2 (13)	6 (15)	2 (40)	3 (10)	0	8 (16)
Diabetes duration‡‡, median years (IQR)	11.3 (8.6-15.0)	11.3 (6.8-14.4)	7.5 (7-14.9)	11.9 (8.6-16.8)	11.3 (10.1-11.6)	10.9 (7.3-14.9)
HbA1c mean						
Pre-certification, mmol/mol ± SD (% ± SD)	54.5 ± 9.6 (7.1 ± 0.9)	54.4 ± 8.8 (7.1 ± 0.8)	53.6 ± 8.7 (7.1 ± 0.8)	57.1 ± 10.4 (7.4 ± 1.0)	55.7 ± 7.4 (7.2 ± 0.7)	55.0 ± 9.7 (7.2 ± 0.9)
Post certification, mmol/mol ± SD (% ± SD)	57.3 ±9.2 (7.4 ± 0.9)	55.2 ± 9.7 (7.2 ± 0.9)	49.4 ± 7.4 (6.7 ± 0.7)	57.7 ± 9.8 (7.4 ± 0.9)	58.0 ± 7.5 (7.5 ± 0.7)	55.1 ± 9.6 (7.2 ± 0.9)
Paired t-test	0.2557	0.5387	0.1861	0.7217	0.1181	0.9606
Duration of follow-up, median years (IQR)	6.6 (5.0-6.8)	5.0 (2.7-6.7)	3.6 (1.6-3.7)	5.3 (2.9-6.7)	6.2 (5.6-6.4)	4.3 (7.3-14.9)

Footnote: †15 of the 49 pilots recorded values in the low red range; ‡39 of the 49 pilots reported values in the low amber range; §5 pilots reported no values outside of the desired green range; ¶29 of the pilots recorded readings in the high amber range; ††3 of the 49 pilots documented values in the high red range. Most pilots reported out-of-range values in more than one subcategory, so their demographic details were analysed in all relevant subgroups. ‡‡Duration of diabetes from diagnosis to 31st December 2019.

Table 3: Total, pre-flight and in-flight capillary blood glucose measurements for all 49 pilots, class 1 and class 2, recorded between May 2012 and December 2019.

		Capillary Blood Glucose Measurements (n)	Percentage (%)
Total capillary glucose measurements, mmol/L (mg/dL)	<4.0 (<72)	48	0.12
	4.0-4.9 (72-89)	550	1.42
	5.0-15.0 (90-270)	37729	97.69
	15.1-20.0 (271-360)	288	0.75
	>20.0 (>360)	6	0.02
	Total:	38621	
Pre-flight capillary glucose measurements, mmol/L (mg/dL)	<4.0 (<72)	34	0.21
	4.0-4.9 (72-89)	291	1.78
	5.0-15.0 (90-270)	15918	97.26
	15.1-20.0 (271-360)	119	0.73
	>20.0 (>360)	4	0.02
	Total:	16366	
In-flight capillary glucose measurements, mmol/L (mg/dL)	<4.0 (<72)	14	0.07
	4.0-4.9 (72-89)	259	1.16
	5.0-15.0 (90-270)	21811	98.00
	15.1-20.0 (271-360)	169	0.76
	>20.0 (>360)	2	0.01
	Total:	22255	
Total out-of-range capillary glucose measurements (<5.0 or >15.0 mmol/L; <90 or >270 mg/dL)		892	2.31
Total amber range capillary glucose measurements (4.0-4.9 or 15.1-20.0 mmol/L; 72-89 or 271-360 mg/dL)		838	2.17
	Pre-flight Amber	410	1.06
	In-flight Amber	428	1.11
Total red range capillary glucose measurements (<4.0 or >20.0 mmol/L; <72 or >360 mg/dL)		54	0.14
	Pre-flight Red	38	0.10
	In-flight Red	16	0.04

Table 4: The number (n) of out-of-range measurements and the frequency (%) with which they occurred for each of the specified blood glucose ranges in relation to the flight time

	Low Red (<4.0 mmol/L; <72 mg/dL), n (%)	Low Amber (4.0-4.9 mmol/L; 72-89 mg/dL), n (%)	High Amber (15.1-20.0 mmol/L; 271-360 mg/dL), n (%)	High Red (>20.0 mmol/L; >360 mg/dL), n (%)	Total Out-of-Range, n (%)
Total Out-of-Range Values	**48 (5.4)**	**550 (61.6)**	**288 (32.3)**	**6 (0.7)**	**892 (100)**
Total Pre-Flight	**34 (70.8)**	**291 (52.9)**	**119 (41.3)**	**4 (66.7)**	**448 (50.2)**
<2 Hours Before Take-Off	24 (50.0)	152 (27.6)	48 (16.7)	2 (33.3)	226 (25.3)
<30 Minutes Before Take-Off	10 (20.8)	139 (25.3)	71 (24.7)	2 (33.3)	222 (24.9)
Total In-Flight	**14 (29.2)**	**259 (47.1)**	**169 (58.7)**	**2 (33.3)**	**444 (49.8)**
Hour 1	4 (8.3)	98 (17.8)	46 (16)	0	148 (16.6)
Hour 2	1 (2.1)	45 (8.2)	27 (9.4)	0	73 (8.2)
Hour 3	2 (4.2)	18 (3.3)	14 (4.9)	0	34 (3.8)
Hour 4	2 (4.2)	14 (2.5)	7 (2.4)	0	23 (2.6)
Hour 5	0	7 (1.3)	2 (0.7)	0	9 (1.0)
Hour 6	1 (2.1)	5 (0.9)	3 (1.0)	0	9 (1.0)
Hour 7	0	1 (0.2)	4 (1.4)	0	5 (0.6)
Hour 8	0	0	1 (0.3)	0	1 (0.1)
Hour 9	0	0	0	0	0
Hour 10	0	0	1 (0.3)	0	1 (0.1)
Hour 11	0	1 (0.2)	0	0	1 (0.1)
Hour 12	0	0	0	0	0
Pre-landing	4 (8.3)	70 (12.7)	64 (22.2)	2 (33.3)	140 (15.7)

Figures

Figure 1: Pre-flight and in-flight blood glucose measurements for all pilots. Max & min (whisker), 5th-50th percentile (black), 50th- 95th percentile (white) and asterix (red) representing the number of in-flight low red values.

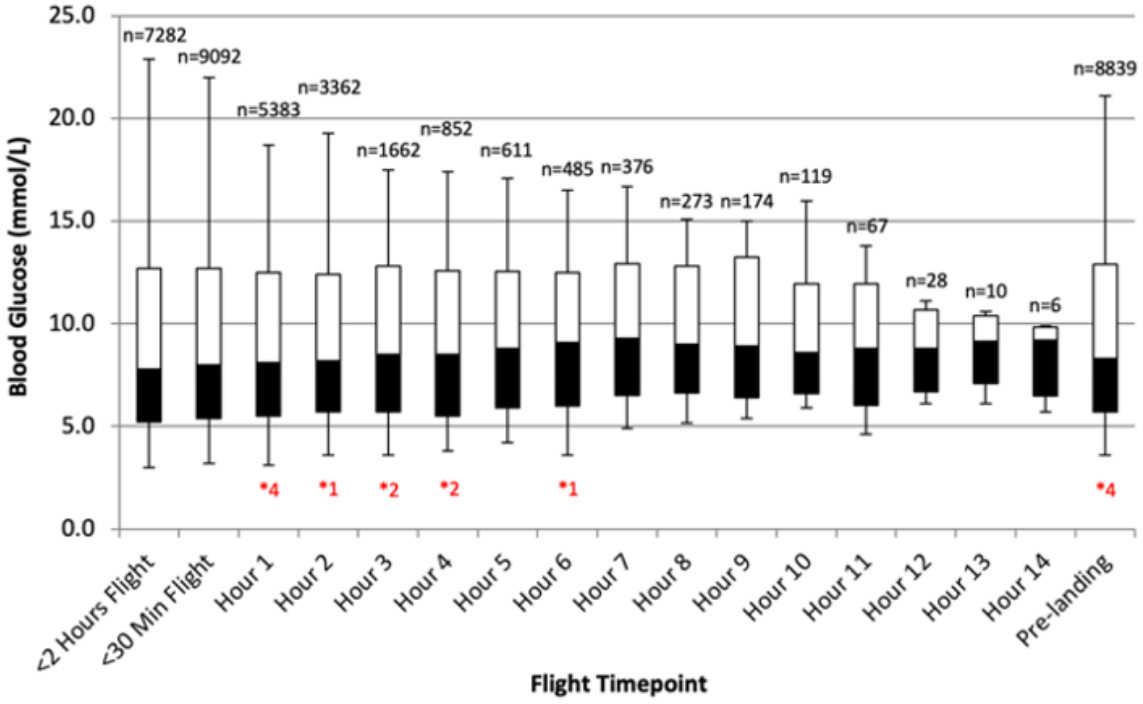


Figure 2: Scatter graphs showing serial capillary blood glucose concentrations after those recorded in the 30 minutes before the flight: (A) a low red value (<4.0 mmol/L; <72 mg/dL), (B) a low amber value (4.0-4.9 mmol/L; 72-89 mg/dL), and (C) a high amber value (15.1-20.0 mmol/L; 271-360 mg/dL)

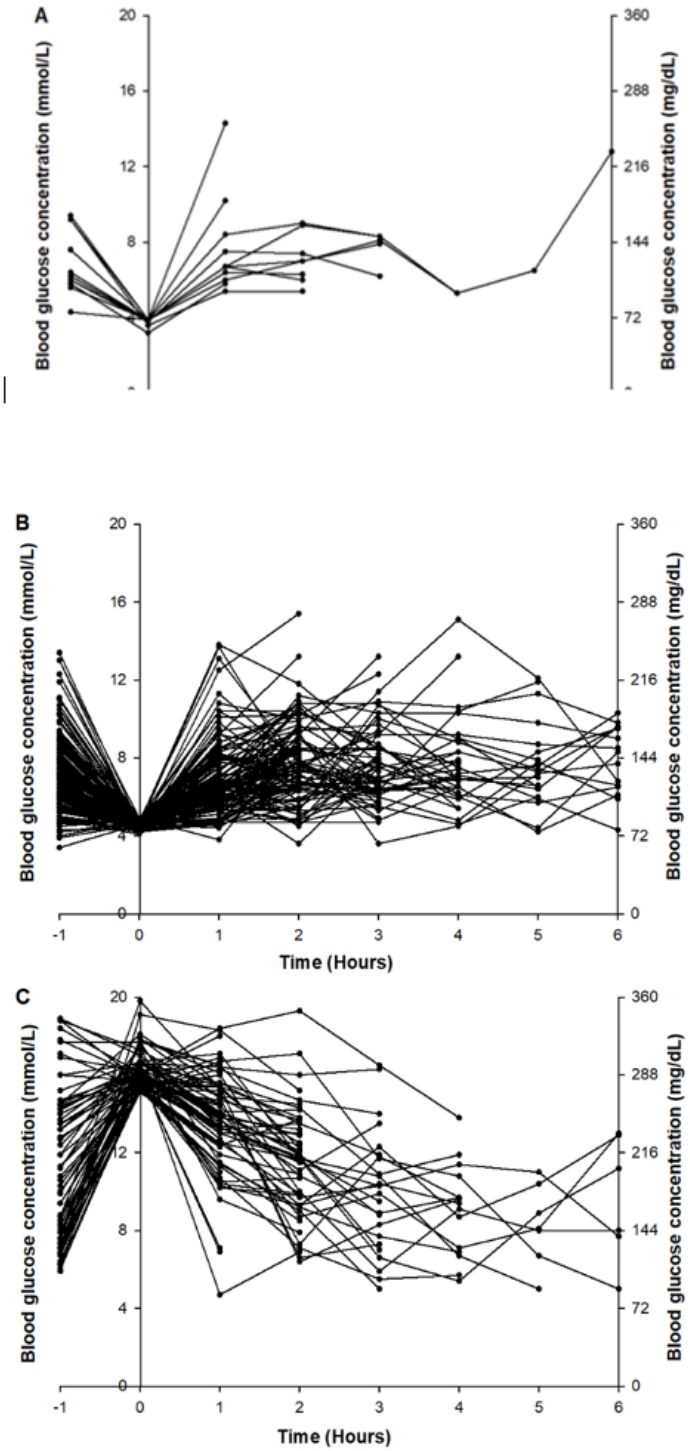


Figure 3: Scatter graphs showing capillary blood glucose concentrations recorded in-flight before and after: (A) a low red value (<4.0 mmol/L; <72 mg/dL), (B) a low amber value (4.0-4.9 mmol/L; 72-89 mg/dL), and (C) a high amber value (15.1-20.0 mmol/L; 271-360 mg/dL)

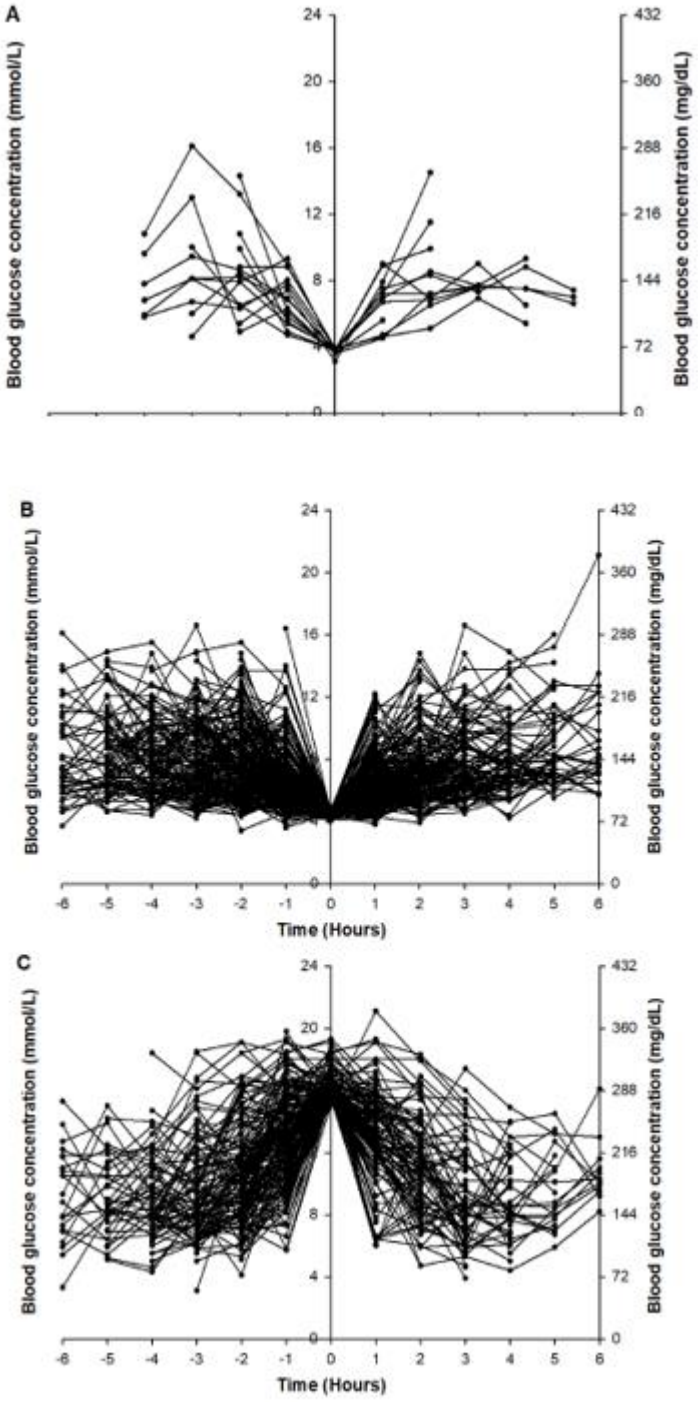


Figure 4: Rate of fall (A) and recovery (B) in mean blood glucose concentration in relation to a low red range value (<4.0 mmol/L; <72 mg/dL) (red), or a low amber range value (4.0-4.9 mmol/L; 72-89 mg/dL) (blue) recorded anytime during the duty period with polynomial trend lines and error bars

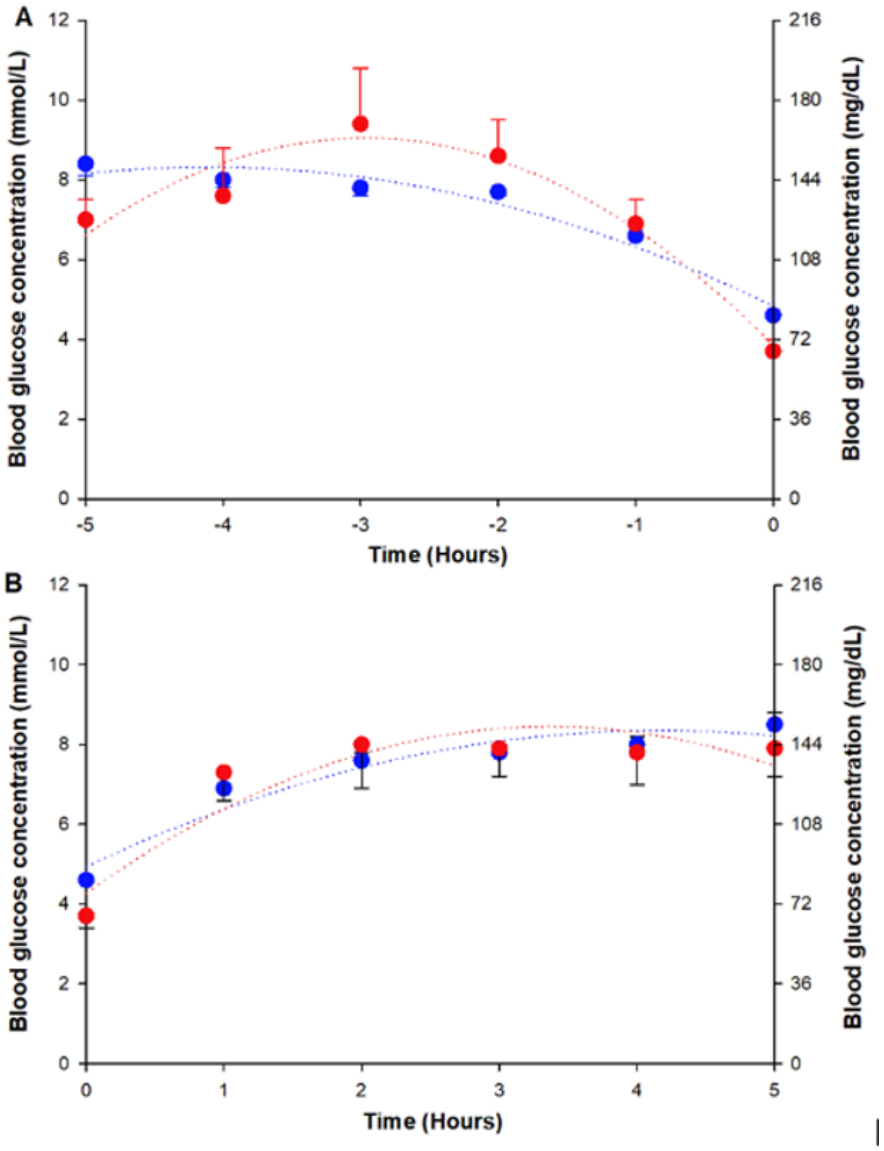
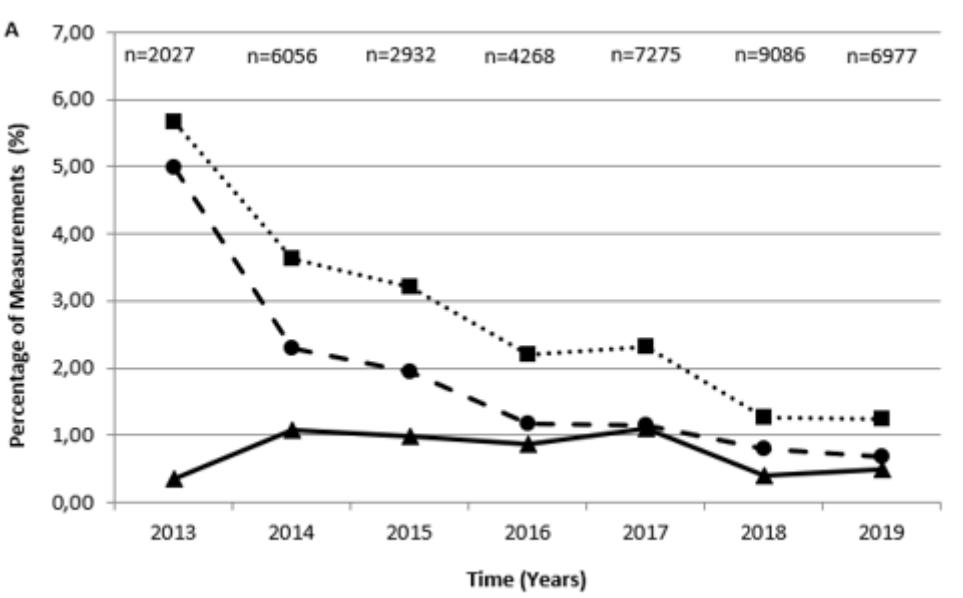
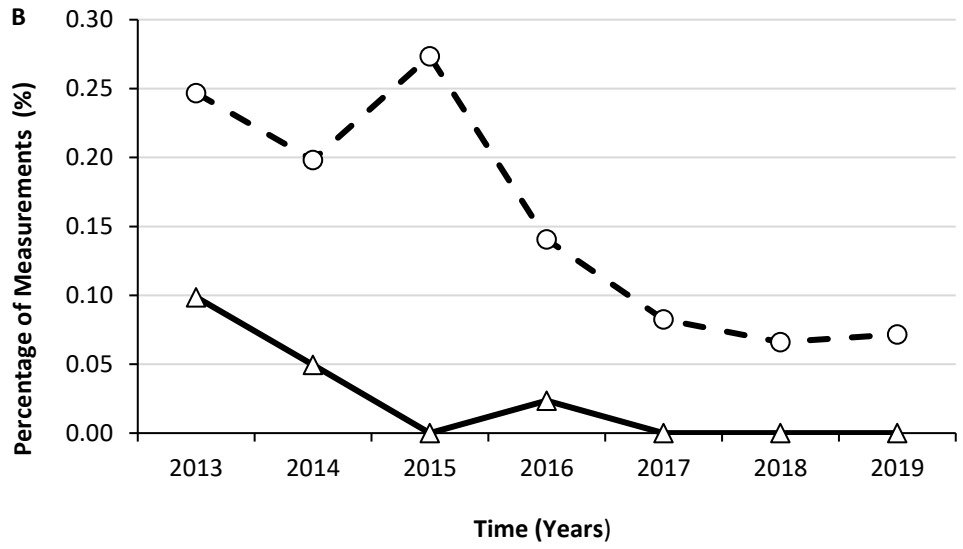


Figure 5A: Overall rate of out-of-range readings for all pilots per year (dotted line with black squares), rate of low amber (4.0-4.9 mmol/L; 72-89 mg/dL) (dashed line with black circles), and high amber (15.1-20.0 mmol/L; 271-360 mg/dL) (solid line with black triangles).[1]
Figure 5B: Rate of low red (<4.0 mmol/L; <72 mg/dL) (dashed line with white circles), and high red (>20.0 mmol/L; >360 mg/dL) (solid line with white triangles).

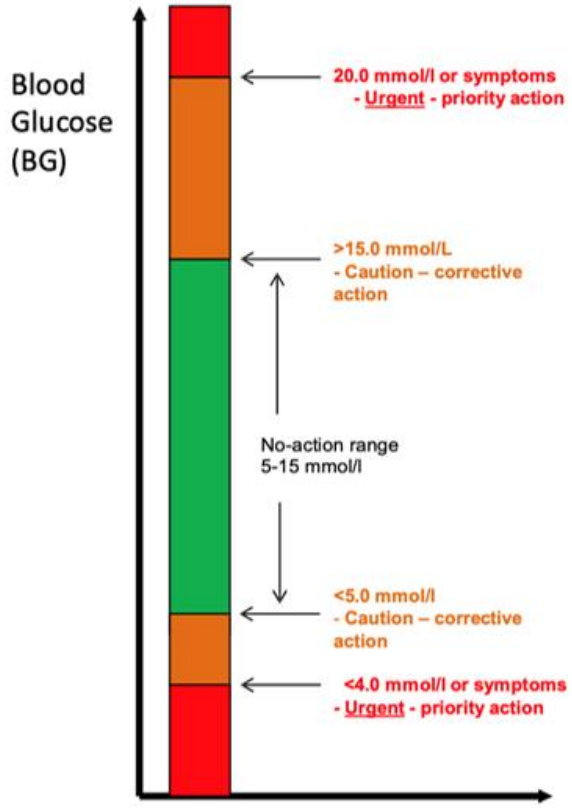




[1] The percentage of measurements was the total CBG values recorded per year. The percentage therefore changes each year depending on the number of CBG values performed. This graph shows that of all the CBG values performed each year, the percentage of those readings that fell outside the acceptable green range declined over time. 0% means that of all the CBG values recorded in those years, none were within the high red, hyperglycaemic range.

Appendix:

The ARA.MED.330 diabetes protocol traffic light system for blood glucose interpretation used to determine acceptable and unacceptable blood glucose ranges and provide direction for appropriate corrective action where necessary.



High Readings

Priority Action (>20.0mmol/l)
1) Repeat reading (+/- check CGMS)
2) Shall hand over duties or if solo pilot consider landing as soon as practicable
3) Otherwise, take appropriate insulin and/or modify CHO intake
4) Resume full duties when BG <20.0mmol/l

Corrective Action (>15.0mmol/l)
1) Repeat reading (+/- check CGMS)
2) If still >15.0mmol/l review insulin dosing and/or modify planned CHO intake

Low Readings

Priority Action (<4.0mmol/l)
1) Repeat reading (+/-check CGMS)
2) If still <4.0mmol/l shall hand over duties or if solo pilot consider landing as soon as practicable.
3) Ingest 10-15g readily absorbed CHO and retest after 15mins
4) Review insulin dosing and/or modify CHO intake
5) If test after ingestion is still <4.0 then ingest further 10-15g CHO and retest after 15 min
6) Wait for 45 mins after the BG returns to the 'green 'range before resuming duties. (In the unlikely event of any symptoms of cognitive impairment the pilot/ATCO should not resume duties for the duration of the flight/control duty period).
7) If crew assistance is required or the pilot becomes incapacitated then a MOR shall be filed

Corrective Action (<5.0mmol/l)
1) Repeat reading (+/- check CGMS)
2) If still <5.0mmol/l ingest 10-15g readily absorbed CHO and retest after 30 mins
3) Review insulin dosing and/or modify CHO intake

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In the above, we have been looking at glucose metabolism and out-of-range readings in pilots with insulin-treated diabetes flying commercial and non-commercial aircraft within the ARA.MED.330 Diabetes Protocol. In the following, we want to look at the practical operation of different glucose measurement techniques in pilots, thereby also studying the role of continuous glucose monitoring systems in aviation.

4. The practical, operational and environmental factors that impact on blood glucose management

Abstract

Introduction

To meet safety requirements, pilots flying under the ARA.MED.330 diabetes protocol are to regularly monitor glucose before and during duty periods. This is in the form of self-monitoring blood glucose (SMBG) which requires pilots' attention. The role of continuous glucose monitoring (CGM) technologies in aviation remains understudied. This study investigated the practical operation and consequences of different glucose measurement techniques by pilots.

Methods

This study is conducted on pilots with diabetes recruited from the SUNDIF trial under the EASA Horizon Europe Work Programme 2021-2022. A 25-item questionnaire was administered to assess pilots' opinions, preferences, and perceptions of SMBG and CGMs. The time required to check glucose levels was recorded during the simulated flight environment and compared between devices.

Results

All six pilots responded to the questionnaire in full. All participants were male, with a median age of 40 (ranged 20-61). Their CGM sensors included Medtronic Guardian™ 4 (n=3) and Dexcom G6 (n=3). Overall, all users were very satisfied with their CGMs whereas only 20-40% rated very satisfied with aspects of SMBG. CGM systems were most valued for convenience and all users stated a preference for CGM over SMBG. The use of CGM (6 ± 4.8 seconds) reduces the mean time required to check glucose by 58% compared to SMBG (47 ± 28 seconds).

Conclusion

The integration of CGM systems offers the potential to optimise blood glucose management in aviation. This study demonstrates insulin-dependent pilots' perceptions of glucose monitoring methods and is a practical alternative to SMBG during flights.

4.1 Introduction

Managing health conditions in the aviation industry is crucial to the safe and effective operation of aircraft. With the prevalence of diabetes continuing to rise, more pilots and air traffic control officers (ATCOs) are now facing the challenges presented by diabetes.

There are many different operational skills and aviation environments that pilots and ATCOs have to content with. For example, pilots holding a class 1 commercial licence usually work in multicrewed aircraft. Those who undertake longhaul flights may be one of four pilots on duty to enable adequate rest during the flight. Some commercial pilots also undertake the role of the safety pilot and may not be operational during the entire flight. Others are involved in training pilots to fly and undertake many hours within flight simulators. In contrast pilots who hold a class 2 private pilots licence will often perform solo flights. Some private pilots own their own aircraft which they need to manually remove from the hanger and prepare prior to flight and then return to the hanger again after landing both of which can be arduous tasks and have the potential to impact on the individual's blood glucose concentration as a result. Some pilots with a class 2 license operate hot air balloons or gliders the working environment for both being quite different to that of an aircraft. Additionally there are also helicopter pilots who again have different set of occupational challenges often needing both hands on the controls. ATCOs, on the other hand, work in control towers on the ground and are principally responsible for managing the flow of aircraft into and out of the airport airspace safely and guiding pilots during take-off and landing. Maximum concentration is required at all times to simultaneously co-ordinate multiple aircraft.

Both commercial pilots and ATCOs frequently work long hours, including night shifts and weekends with unpredictable meal and rest breaks. Pilots also have to content with changes in time zone. These occupational challenges can make it difficult to maintain a stable blood glucose concentration throughout the duty period. Furthermore, delays in take-off and landings and limited on-board refreshments can increasing the challenge. Pilots who are either flying solo or who are required to manually operate an aircraft may have limited windows to be able to operate additional devices such as a blood glucose monitor or to review their CGM data. Class 2 pilots flying small aircraft, gliders or hot air ballons may have to perform physically strenuous tasks to prepare for take-off which can also influence their glycaemic control during flight. Each aviation worker faces a unique environment within which they work and this must be assessed and dealt with on each and every duty to determine how it might impact on their diabetes management.

One common feature among all pilots is the requirement to undertake finger-stick glucose monitoring and any necessary action for blood glucose results outside of the satisfactory range in accordance with the ARA.MED.330 diabetes protocol. This is a stipulation of their medical licence regardless of pilot class, operational tasks, and the environmental constraints imposed. If this cannot be performed in additional to their occupational duties for whatever reason, then the risk of potential incapacitation cannot be determined and their medical license will be revoked. For ATCOs, presently they are deemed unfit if they require insulin to treat their diabetes. Therefore, due to their use of oral and or subcutaneous antihyperglycaemic agents, their risk of hypoglycaemia is significantly lower and the frequency of blood glucose monitoring is adjusted to reflect this. However, they are also subject to strict adherence of two hourly glucose monitoring while on duty and any non-compliance with the protocol poses a risk to public safety.

Frequent blood glucose monitoring during duty periods is key to reducing the risk of pilot incapacitation and maintaining the strictest of safety standards. Both long and short-term consequences of diabetes can interfere with aviation safety. Short-term complications like hypoglycaemic or hyperglycaemic episodes can cause cognitive impairment of variable severity, seizures and loss of consciousness. However, these are rarely sudden occurences and almost always have warning symptoms, allowing patients to take action before they become incapacitated. So, while it remains a potential hazard when piloting or managing air traffic, actions may be taken swiftly. In addition to performing frequent blood

glucose monitoring, pilots and ATCOs with diabetes must also pass strict requirements, including hypoglycaemia awareness assessment, blood and urine analysis and cardiovascular and retinopathy screening, set out by the aviation regulators before being permitted to fly[3,4].

Traditionally, blood glucose monitoring has been achieved by a 'finger prick' and a hand-held blood glucose monitoring system to measure the capillary glucose concentration. In recent years, CGM systems have revolutionised diabetes management, improving glycaemic control and reducing the risk of diabetes-related complications. CGM systems use disposable sensors attached to the skin which measure the glucose concentration in the interstitial fluid displaying the real-time value on users' electronic hand-held devices, smart phones and smart watches. In metabolic steady states, interstitial fluid and blood glucose measurements deliver almost identical values. However, in rapidly changing glucose levels, the measurements of interstitial glucose values are known to lag behind capillary samples[5]. This difference is known as physiologic time delay and may be affected by local physiology and metabolic activity of the surrounding tissues. CGMs otherwise have a comparable aggregate mean absolute relative difference (MARD) to SMBG and patients generally prefer using CGM.[6,7]

There are a number of advantages of using CGM systems over SMBG. They provides a more convenient means of monitoring glucose, without the need to draw blood and associated pain, and reducing the time it takes to review the results. Furthermore, CGM systems show data on glucose trends and have arrows to show the direction of glucose change. Additionally, built in alarms alert the user when glucose levels are approaching hyper- and hypoglycaemic ranges or when blood glucose concentration is rising or falling quickly to enble intervention prior to the blood glucose reaching dangerously low or high ranges. These features may be of great use to all pilots and ATCOs as it would reduce the effort and time required to monitor their glucose levels while providing an extra safety net to reduce the risk of hypo- or hyperglycaemic events. Nevertheless, not necessarily all types of operations pilots might be able to fly following the stringent protocol requirements of blood glucose monitoring on their occupacional duties. For those other mitigation measures and limitations might be taken in consideration.

CGM systems may also provide additional benefits to healthcare teams and regulation authorities. Because the CGM system provides a continuous measurement of the glucose concentration it will detect any episodes of hypoglycaemia whether the user has symptoms or not therefore detecting hypoglycaemia unawareness. Moreover, safety features of CGM systems prevent the user from manually modifying the blood glucose readings. CGM systems also typically allow the user to record events, carbohydrates and insulin doses alongside the blood glucose concentration readings which offers insight into associated events and patterns with any out-of-range recordings while maintaining data integrity for better clinical interpretation of measurements.

However, working within the aviation industry poses unique challenges for pilots and ATCOs as discussed earlier which may impact on their willingness and ability to adopt and use CGM systems effectively.[8,9] The present study aims to investigate the attitudes of pilots and ATCOs with diabetes on the use of CGM systems as a vital tool for diabetes management within aviation.

Understanding the views of pilots and their attitudes towards glucose monitoring systems is crucial to gain valuable insights into the perceived benefits and barriers of using these systems in an aviation setting. This may highlight the challenges pilots, and ATCOs, face and can aid the development of support and education programmes as well as contribute towards refining current aviation medical requirements for those with diabetes. Hence, this study aims to assess the attitudes and preferences of insulin-dependent pilots towards the method of glucose monitoring.

4.2 Methods

This project was conducted in conjunction with the Safe Use of New technologies in Diabetes in Flight (SUNDIF) study funded by the EASA HORIZON grant (IRAS 31859; protocol number FHMS 2022 15). Inclusion criteria for the SUNDIF trial included: diagnosis of type 1 diabetes, diagnoseis must be greater than 12 months, currently on insulin pump therapy, aged between 18-65 years, Body-Mass-Index of <30 kg/m^2,HbA1c of <9%, able to undertake long haul airliner flight, and does not suffer from any cardiovascular, respiratory, or ENT diseases.

Pilots participating in the study were surveyed for their opinions and preferences on using SMBG and CGM. All six pilots were routinely using CGM to monitor their glucose. Their CGM systems brand was also recorded. Participants were observed measuring their glucose levels using both methods, and the mean time taken was calculated.

A 25-item voluntary questionnaire was designed and provided to pilots participating in the SUNDIF study. The details of the questionnaire are shown in **Table 1**.

The questionnaire focused on the following:

1) Attitudes towards their CGM systems: Overall, Effort, Ease of use, Convenience, Accuracy
2) Attitudes towards and trust in SMBG
3) The value of information offered by CGM and SMBG
4) The time it takes to check blood glucose levels via CGM and SMBG

Physical copies of the questionnaires were provided to pilots with type 1 diabetes on insulin pump therapy during their visits to undergo the SUNDIF trial. To ensure accurate and representative time measurements, authors AM and KSF recorded the time taken for pilots to perform the glucose checks in the hypobaric chamber of the SUNDIF study. All pilots were observed using their own CGM systems as they were adept at using them.

Results

All six pilots in the study responded to the questionnaire in full. The median age of the pilots was 40 (ranged 20-61) years. All participants were male. All participants used a CGM system, 3 used Guardian 4 and 3 used Dexcom G6. All pilots used an insulin pump: Medtronic 780G (n=3; Medtronic MiniMed, California, USA), Tandem T-Slim X2 (n=1; Tandem Diabetes Care, California, USA), Omnipod Dash (n=1; Insulet, Massachusetts, USA), and mylife YpsoPump (n=1; Ypsomed, Burgdorf, Switzerland).

All users report being very satisfied with CGM overall, with all responses being either satisfied or very satisfied. Attitudes towards SMBG remain variable, with less than half of the responses being very satisfied. Some users were dissatisfied with the effort required, ease of use and convenience. Attitudes towards CGM and SMBG are demonstrated in **Figure 1**.

Pilots' trust in the results provided by CGM and SMBG and their confidence in being able to act appropriately to results are illustrated in **Figure 2**. Users report being more confident in how to act upon CGM results and having higher overall trust. All users trust CGM and SMBG at least a moderate amount. Most aspects of CGM were aspects valued for convenience (**Figure 3**). All users valued the actual glucose measurements, trend arrows, trend graphs and high/low glucose alerts. The value of the low glucose alarm and downloadable data were variable. All users stated they preferred CGM over SMBG.

The glucose monitoring time of CGM is shorter than SMBG, with the mean time required being 6 (± 4.8) and 47 (± 28) seconds respectively. The longest amount of time taken to use CGM was 20 seconds, compared to 120 seconds for SMBG.

4.3 Discussion

There are currently a handful of aviation protocols that allow insulin-dependent pilots to fly. These all involve in-depth clinical evaluations, including the standard diabetic biochemical and lipid profiles, screening of diabetic complications and detailed assessments of hypoglycaemic awareness, glycaemic thresholds and glucose monitoring records[9].

Previous studies have evaluated the use of blood glucose monitoring systems at altitude and demonstrated some degree of overestimation of glucose levels[12]. This is in addition to other environmental or operator-related limitations during the flight that may affect the accuracy of these hand-held systems[13]. Advancements in CGM technologies has since made it a feasible alternative to SMBG as it offers sufficient accuracy[14,15]. Its use at altitude has since been subject to many debates, with many viewing it as an effective method to facilitate in-flight glucose monitoring and also achieving clinically desirable glycaemic targets[16,17].

Specifically, a meta-analysis in 2019 reported that CGMs detect significantly higher number of hypoglycaemic events than SMBG across many studies[18]. However, these episodes were predominantly nocturnal events and may not necessarily result in the same pattern during waking hours. Benefits were observed in other metrics, such as Time In Range (TIR), where CGM reduces the time spent in hypoglycaemia or hyperglycaemia[18,19]. These again would be beneficial outcomes for pilots as they are required to operate within strict glucose ranges to prevent the chances of incapacitation. As reported by our pilots, they all value the actual glucose ranges, glucose trends, and high/low glucose alerts offered by CGM systems. This is reflected in their overall trust and confidence in acting on the results shown in CGM. There is only minor difference between CGM and SMBG in the reported trust and confidence in they should act on the glucose values, suggesting that CGM is viewed as at least equivalent to SMBG.

Another critical aspect to evaluate is patient satisfaction as people living with diabetes must be both satisfied with its accuracy and usability to remain adherent to its use. The consensus identified by the meta-analysis was predominantly high satisfaction and adherence which parallels our findings in this survey[18]. Almost all responses were “very satisfied” with the CGMs overall, with some slightly less satisfied with the effort/attention required, convenience and accuracy. This is contrasted by the more varied responses regarding SMBG, with a few pilots feeling neutral or dissatisfied with the effort/attention required, ease of use and convenience. Considering these factors and the significantly longer time that SMBG requires for measurements, pilots likely prefer CGMs over SMBG. These findings are likely applicable to ATCOs given the similarities in their working conditions.

Currently, Austria, Australia, Canada, Ireland, United Kingdom (UK), and the United States have formulated protocols to allow pilots with diabetes to fly under specific conditions or mitigating measures. In the UK, the protocol, which is run in partnership with Ireland and Austria, requires stringent diabetes management for the issuance of class 1 medical certificates needed to validate commercial pilot licences[11,20]. Of a total of 38,621 capillary glucose measurements, only 14 (0.04%) low red values (<4.0 mmol/L) were recorded in-flight. All except four of these low red measurements were restored to within the green range by the time of the next measurement. These were all adequately self-managed by the pilot without additional assistance by others. There were no episodes of severe hypoglycaemia during the study protocol where a pilot required help for recovery, hence, research should now focus on facilitating the practicalities of in-flight glucose measurements. A further preliminary study on the use of SMBG and CGM has shown promising results. The study compared eight pilots’ CGM readings against pre- and in-flight SMBG measurements, demonstrating strong correlation ($r = 0.743$; $P<0.001$)[21].

With evidence to support the safety of pilots and ATCOs with diabetes, the next challenge to address is optimising and streamlining the processes for measuring glucose. The steps required to prepare and administer the glucose monitoring tests vary greatly and are demonstrated in **Table 2**. The time estimated for each step of using a SMBG and CGM were used here and demonstrated that CGM reduces the time taken away from flying duties by more than half. This difference is more pronounced in the

self-reported results, with CGM reducing the mean time spent on glucose monitoring by 58% compared to SMBG. Over the course of a standard 5-hour flight, the pilot would have to measure their glucose levels at least 7 times when following the protocol used in the UK, Ireland and Austria. These time points include the following: 1 hour before reporting for duty (pre-flight) or 2 hours before flight, within 30 minutes before take-off, hourly during flight and 30 minutes before landing. This would have reduced the time taken away from piloting by at least 90 seconds throughout the flight (only the first two readings occur pre-flight). The time saved is more significant (329 vs 72 seconds) if extrapolated from the pilots' recorded time from our study. This assumption will likely be an underestimation of time saved as pilots will likely measure more frequently than advised, especially around meals and injections.

Limitations

The primary limitation of this study is that operational impact of glucose measurements was measured in simulated settings. As the measurements were based on the environment within a hypobaric chamber, these findings represent the approximate impact of CGM use and future studies may benefit from evaluating the real-time impact on pilots during flights to better understand the impact of opertiaonal conditions such as body movements and aircraft vibrations. While only six pilots were included, studying this exact demographic should provide sufficient validity for our goals. However, the sampling method of studying individuals that were recruited from a clinical trial will likely skew towards those who are particularly motivated, educated, and interested in CGM use[22]. This may result in over-estimation of the optimism towards CGM that not all insulin-dependent pilots and ATCOs share. Also, the length of user-experience of both CGM and SMBG were not included in the survey which may also influence how reliable they find each method or how quickly they use the systems.

4.4 Conclusion

In conclusion, the integration of CGM systems hold tremendous potential for managing diabetes within the aviation industry. The study's focus on insulin-treated pilots' perceptions of glucose monitoring systems is a pivotal step towards addressing potential barriers and harnessing the advantages of these technologies. Although calibration may be required, the convenience and accuracy of CGM systems are perceived by pilots to be better than SMBG and can be further verified in real flight conditions. In view of the stressed and time-pressured environment that pilots face, this adds to its potential in improving the management of diabetes of both pilots and ATCOs in the industry.

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Tables

Table 1. Questionnaire to assess pilots' attitudes and opinions towards Continuous Glucose Monitoring and Self-Monitor Blood Glucose

Regarding your CGM, how dissatisfied or satisfied have you been with:					
	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied	Very Satisfied
1. How accurate it is	1	2	3	4	5
2. How convenient it is	1	2	3	4	5
3. How easy it is to use	1	2	3	4	5
4. How much effort and attention the device requires	1	2	3	4	5
5. How well it works overall	1	2	3	4	5

When using the CGM, how much do you value the following features?				
	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied
1. How accurate it is	1	2	3	4
2. How convenient it is	1	2	3	4

3. How easy it is to use	1	2	3	4
4. How much effort and attention the device requires	1	2	3	4

	Do Not Trust It At All	Trust It A Little	Trust It Moderately	Trust It A Lot
6. Overall, how much do you trust your CGM to do what it is supposed to do?	1	2	3	4

	Not Confident At All	A Little Confident	Moderately Confident	Very Confident
7. Overall, how confident are you that you know what to do with the CGM numbers, trends, arrows and other information that you see on the receiver?	1	2	3	4

		No, not at all	A little	A moderate amount	I value this feature a great deal
8a.	The actual glucose numbers	1	2	3	4
8b.	The trend arrows	1	2	3	4
8c.	The trend graph	1	2	3	4
8d.	The high/low alerts	1	2	3	4
8e.	The “fixed low” alarm (when glucose levels drop below 55 mg/dl)	1	2	3	4
8f.	Review of the downloaded CGM data	1	2	3	4

How long does it take to check your blood glucose levels via CGM (includes taking your device out to getting your measurement): Please record three times below.

_____ Minutes _____ Seconds

_____ Minutes _____ Seconds

_____ Minutes _____ Seconds

Self-Monitoring Blood Glucose (SMBG) Attitudes

Regarding your SMBG, how dissatisfied or satisfied have you been with:

	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied	Very Satisfied
1. How accurate it is	1	2	3	4	5
2. How convenient it is	1	2	3	4	5
3. How easy it is to use	1	2	3	4	5
4. How much effort and attention the device requires	1	2	3	4	5
5. How well it works overall	1	2	3	4	5

	Very Dissatisfied	Moderately Dissatisfied	Neutral	Moderately Satisfied
1. How accurate it is	1	2	3	4
2. How convenient it is	1	2	3	4
3. How easy it is to use	1	2	3	4
4. How much effort and attention the device requires	1	2	3	4

When self-monitoring, how much do you value the following features?

	Do Not Trust It At All	Trust It A Little	Trust It Moderately	Trust It A Lot
6. Overall, how much do you trust your SMBG to do what it is supposed to do?	1	2	3	4

	Not Confident At All	A Little Confident	Moderately Confident	Very Confident
7. Overall, how confident are you that you know what to do with the SMBG numbers?	1	2	3	4

	No, not at all	A little	A moderate amount	I value this feature a great deal
8a. The actual glucose numbers	1	2	3	4

How long does it take to check your blood glucose levels via SMBG (includes taking your device out to getting your measurement): Please record three times below.

_____ Minutes _____ Seconds

_____ Minutes _____ Seconds

_____ Minutes _____ Seconds

Overall experience of CGM: Poor 1 2 3 4 5 Excellent

Overall experience of SBGM: Poor 1 2 3 4 5 Excellent

Overall preference: CGM device / No preference / SMBG

Table 2. The steps and estimated time required to conduct capillary glucose measurements

Steps	SMBG	CGM
Retrieve kit	5 seconds	5 seconds
Turn on the device	2 seconds	2 seconds
Open measurement strip packaging	2 seconds	-
Insert measurement strip into device	2 seconds	-
Open alcohol wipe	2 seconds	-
Clean finger with alcohol wipe	2 seconds	-
Prime and use lancet	2 seconds	-
Capture blood on strip	2 seconds	-
Await results	5 seconds	2 seconds
Read and interpret results	2 seconds	2 seconds
Time required based on estimations		
Estimated time for one measurement	26 seconds	11 seconds
Estimated total time required across a 5-hour flight	182 seconds	77 seconds
Time required based on pilots' mean time required		
Pilots' mean time for one measurement	47 seconds	6 seconds
Estimated total time required across a 5-hour flight	329 seconds	72 seconds

SMBG: Self-Monitoring Blood Glucose; CGM: Continuous Glucose Monitoring

Figures

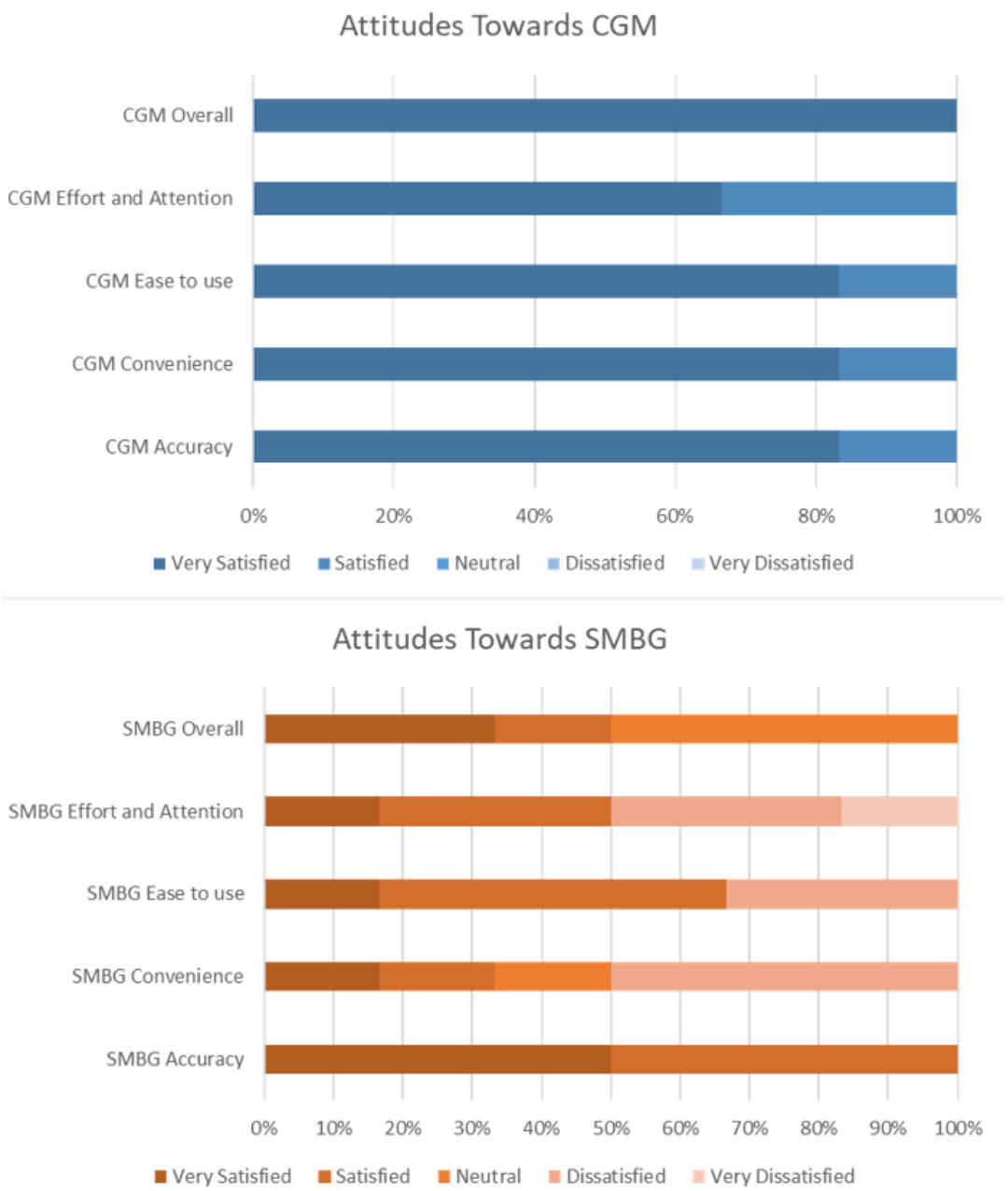

Figure 1. Pilots' attitude towards Continuous Glucose Monitoring (CGM) and Self-Monitoring of Blood Glucose (SMBG)
CGM: Continuous Glucose Monitoring; SMBG: Self-Monitoring of Blood Glucose

Figure 2. Pilots' trust in the glucose values provided by their devices and their confidence in being able to act on results appropriately
CGM: Continuous Glucose Monitoring; SMBG: Self-Monitoring of Blood Glucose

Figure 3. Additional convenience metrics of Continuous Glucose Monitoring systems

5. Diabetes complications

This document provides a detailed review of all modalities to evaluate and characterize macrovascular and microvascular complications needed to risk-stratify Pilots and ATCOs with diabetes. The present document was prepared following the most recent Standards of Care from the American Diabetes Association [1] integrated by specific guidelines or systematic reviews issued by scientific associations specifically dedicated to interested systems as listed in the references.

A meeting with the CaVD study team has taken place and an agreed method for assessing cardiovascular risk in pilots and ATCOs was determined. This study is currently underway as part of the Horizon project and the findings will be presented in a later deliverable.

Macrovascular complications
In asymptomatic individuals, routine indiscriminate screening for coronary artery is not considered cost-effective as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated and, therefore, is not recommended.

Cardiac Testing is based on: Exercise ECG testing, Echocardiography, CRT or MRI-based Coronary Calcification Scoring (CCS), CT- or MRI-based non-invasive Coronary Angiography, Pharmacologic Stress Echocardiography, Cardiac Nuclear Imaging, Cardiac Computerized Tomography Angiography (CCTA). Stress Cine-MRI and Stress Perfusion MRI [2].

Candidates for advanced or invasive cardiac testing include those with typical or atypical cardiac symptoms and an abnormal resting electrocardiogram (ECG).

Exercise ECG testing without or with echocardiography may be the initial test.

In adults with diabetes >40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Echocardiography or nuclear imaging should be considered in individuals with diabetes whose resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities).

In addition, individuals who require stress testing and cannot exercise should undergo pharmacologic stress echocardiography or nuclear imaging. There is also evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies [3].

Another macrovascular complication is represented by Peripheral Artery Disease (PAD), with progressive obstructive manifestations and diffuse arterial wall calcifications.

Initial screening should include an assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Further investigation should include an ankle-brachial index in the presence of leg fatigue, claudication with decreased or absent pedal pulses, and rest pain requiring grief therapy. Ultrasound scan of large abdominal and limb arteries will follow as appropriate, with computed tomography-based angiograms if needed or Toe Systolic Blood Pressure (TSBP) in search of a <30 mmHg value (as part of foot ulceration preventive/management strategies).

Consequences for Pilots and ATCOs: medical assessors should manage cardiovascular problems, following MED.B.010 and ATCO.MED.B.010 rules, as they do with the other flight professionals by considering that diabetes makes them more severe and paying special attention to coronary artery disease and arrhythmias. However, before cardiovascular problems come into play, they should consider the additive CR risk due to DM by using the SCORE2-Diabetes Risk Calculator,which is recommended to estimate up to 10-year cardiovascular risk in pilots and ATCOs with diabetes.

Microvascular complications
Diabetic Retinopathy
Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist within five years after the onset of diabetes. People with type 2 diabetes should have an initial dilated and thorough eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis.. After the initial eye examination, an annual eye examination is recommended, but the frequency can be decreased to every two years in case of no evidence of diabetic retinopathy (DR) and good glycaemic control.

Screening for DR is an essential, cost-effective aspect of diabetes management. The current guidelines suggest a screening vision examination (before pupil dilation if this is necessary) and a retinal examination adequate for DR classification, including (1) direct or indirect ophthalmoscopy or slit-lamp biomicroscopic examination of the retina, (2) retinal (fundus) photography, and dilated or non-dilated photography with or without accompanying Optical Coherence Tomography (OCT). Fluorescein angiography is not required for diagnosis but helps evaluate neovascularization, microaneurysms, or macular capillary nonperfusion areas.

The classic retinal lesions of DR include microaneurysms, intraretinal hemorrhages, venous beading (venous caliber changes consisting of alternating areas of venous dilation and constriction), intraretinal microvascular abnormalities, hard exudates (lipid deposits), and retinal neovascularization.

The stages of DR can be categorized using the simple International Classification of DR Scale [4] into Non-Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR) and Diabetic Macular Edema (DME). NPDR progresses from mild to moderate and severe DR through a spectrum of the above-mentioned vision-threatening lesions. PDR is the most advanced stage, depending on the angiogenic response to extensive capillary ischemia with new vessels developing on the disc or along the vascular arcades, most often at the interface between perfused and nonperfused retinal areas. DME can be seen at any DR severity level and can run an independent course. It is classified based on a clinical examination or retinal photography results according to its proximity to fovea updated with information from OCT into (1) no DME, (2) non-center-involving DME, and (3) center-involving DME.

Since advanced stages of DR and DME may be present even in patients not experiencing visual symptoms, this classification allows us to predict the risk of DR progression and visual loss and thus determine the appropriate referral, follow-up intervals, and treatment recommendations.

Consequences for Pilots and ATCOs: medical assessors should manage eye defects, as expected in people without diabetes following MED.B.070 and ATCO.MED.B.070 rules, paying special attention to visual acuity and diplopia.

Diabetic Kidney Disease (DKD)
At least annually, urinary albumin (UACR, e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate (eGFR) should be assessed in people with type 1 diabetes with a duration of >5 years and in all people with type 2 diabetes regardless of treatment.
Cystatin C (another marker of eGFR) is also suggested in combination with the serum creatinine to support clinical decisions better. Normal albuminuria is defined as <30 mg/g creatinine, moderately elevated albuminuria as 30–300 mg/g creatinine, and severely elevated albuminuria as >300 mg/g creatinine in two of three specimens of UACR collected within a 3- to 6-month period. However, as UACR is a continuous measurement, differences within ranges are associated with renal and cardiovascular outcomes [5]. According to the diabetes-specific CKD-EPI formula, eGFR is expressed as ml/min/1.73 m^2 and computed from serum creatinine concentrations combined with age and gender (without race nowadays). It ranges from normal (G1; >90) to decreased: mildly (G2; 60-89), mildly to moderately (G3a;

45-59), moderately to severely (G3b; 30-44), severely decreased (G4; 15-29), and kidney failure (G5; <15).

DKD diagnosis is usually clinical and based on elevated UACR or reduced eGFR without gross hematuria or signs/symptoms of other primary causes of kidney damage and in the presence of retinopathy. Active urinary sediment (i.e., containing red or white blood cells or cellular casts) with rapidly increasing albuminuria/proteinuria or rapidly decreasing eGFR or the presence of nephrotic syndrome (without RD in type 1 diabetes) suggests referral to a nephrologist for further diagnosis, including kidney biopsy if needed.

- *Consequences for Pilots and ATCOs*: medical assessors should manage renal problems manage renal problems as expected in people without diabetes, following MED.B035 and ATCO.MED.B.035 rules. by considering that diabetes makes them worsen more rapidly except for treatment regimens including kidney-protective drugs (like glifozins or GLP1-receptor agonists).

Diabetic Neuropathy (DN)
Diabetic neuropathy (DN), with 50% of cases being asymptomatic, encompasses a heterogeneous group of disorders with diverse clinical manifestations warranting appropriate management for the patient's overall long-term quality of life. It reflects ischemic insult to nerve-nourishing micro-vessels (i.e., "vasa nervorum") besides direct nerve damage. Its diagnosis is by exclusion.

Symptoms vary according to the class of sensory fibers involved, the most common and early reflecting damage to small fibers and including pain and dysesthesia (unpleasant sensations of burning and tingling). Large fibers may also be involved, thus causing numbness and loss of protective sensation (LOPS) due to distal sensorimotor polyneuropathy.

Its most frequent presentations are Diabetic Peripheral Neuropathy (DPN), Diabetic Autonomic Neuropathy (DAN), and Diabetic Foot (DF), manifesting as slow-healing ulcers eventually leading to amputations, especially in the absence of adequate foot care.

Individuals with a type 1 diabetes duration >5 years and all individuals with type 2 diabetes should be assessed annually for DPN and DAN using simple clinical tests, including pinprick and hot/cold testers for small-fiber function investigation (pain and thermal sensation), as well as, (a) Achilles reflex triggering and ankle-toe tuning-fork or biothesiometer-based testing for sensitivity and vibration investigation and (b) four-site 10-g mono-filament touch/pressure test for protective sensation analysis, with an eye to large-fiber function defects.

The medical history is also crucial in search of night-worsening sleep-disruptive pain, described as burning, painful cold, lancinating, tingling, stabbing, or shooting, possibly integrated by an 11-point numeric rating scale (Likert scale) or a visual analog scale, as well as, the "Douleur Neuropathique en 4 Questions" (DN4-Interview). Other patient-reported discomforts may be non-painful paresthesia (tingling, prickling, or ant-like sensations), dysesthesia (spontaneous or evoked unpleasant abnormal sensation), sensory ataxia (ataxic gait), or numbness (often described as ''wrapped in the wool"), sometimes coming with hyperalgesia (exaggerated response to painful stimuli) and allodynia (pain triggered by ordinarily non-painful stimuli).
The symptoms and signs of DAN should be part of the investigation in search of cardiovascular manifestations (Cardiovascular Autonomic Neuropathy. CAN, i.e., resting tachycardia, orthostatic hypotension), gastrointestinal changes (Gastrointestinal Neuropathies, GIN, i.e., gastroparesis, constipation, diarrhea, fecal incontinence), genito-urinay defects (Genito-Urinary Neuropathy, GUN, i.e., Lower Urinary Tract Symptoms [LUTS], including nocturia, frequent urination, urination urgency, weak urinary stream, recurrent urinary tract infections, neurogenic bladder, decreased female sexual desire, male erectile dysfunction), sudomotor changes (Sudo-Motor Neuropathy, SMN, i.e., increased or decreased sweating), sympathetic system reaction defect (SSRD, i.e., hypoglycaemia unawareness).

Tests include: (i) for CAN, Electrocardiographic (ECG) recording for Resting Tachycardia (>100 bpm), Heart Rate Variability (HRV), and Deep Breathing (DB), as well as Lying-to-Standing Blood Pressure (BP) Monitoring in search of a >20 mmHg systolic BP or >10 mmHg diastolic BP fall without compensatory heart rate (HR) increase; (ii) for GIN, gastric emptying examination through scintigraphy of digestible solids at 15-min intervals for four h after food intake or radio-labeled octanoic acid breath test and esophagogastro-duodenoscopy/colonoscopy as needed; (iii) for GUN, clinical examination in search of a palpable bladder integrated by urodynamic tests and validated gender-oriented sexual function questionnaires; (iv) for SMN, qualitative or quantitative computed sweat testing still waiting for full validation like Neuropad indicator test or Sudoscan measuring electrochemical skin conductance.

Consequences for Pilots and ATCOs: medical assessors should manage neuropathy following MED.B.065 and ATCO.MED.B.065 rules paying special attention to recurring episodes of cerebral dysfunction due to hypoglycaemia unawareness, dysesthesia, vascular dysregulation symptoms, and recurrent tachy-arrhythmic episodes.

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6. Overall Conclusions

Review of the literature for best practice available diagnostic methods to evaluate long-term diabetes control

- The use of CGM by ITDM pilots and ATCOs would greatly improve the practicability of on-duty glycaemic control. It would provide an effective method to share results with aeromedical examiners and treating physicians, in order to get timely medical advice concerning glycaemic management. The glucose sensors are a major advance, and depending on the type of the sensor, can provide both a glucose trend and a warning, and can therefore be very helpful during duty.

Glucose monitoring methods and performance at altitude

- The modern CGM systems continue to provide vital support in the management of diabetes for insulin-treated individuals. Its uses may extend to overcoming occupational barriers, particularly for those operating in safety-critical industries like aviation. Our study found that CGM measurements demonstrate a strong to very strong correlation with SMBG and plasma glucose measurements across both ground-level environments and simulated flight conditions with lowered atmospheric pressures. As such, CGMs provide a viable alternative to SMBG within aviation settings.

Published data of people treated with insulin who are allowed to fly

- Insulin-treated pilots were considered to carry unacceptable risks. The introduction of new monitoring systems have shown that risks can be mitigated. No safety concerns have emerged using established protocols, which has allowed pilots, of all classes, (excluding ATCOs) with insulin-treated diabetes to safely undertake complex safety-critical occupational duties. Many countries are now following leading countries in certificating insulin-treated pilots.

An evaluation of glucose metabolism and out-of-range readings in pilots with insulin-treated diabetes flying commercial and non-commercial aircraft within the ARA.MED.330 Diabetes Protocol May 2012-December 2019

- This study demonstrated that with strict adherence to the ARA.MED.330 diabetes protocol pilots and ATCOs with insulin treated diabetes are able to perform their safety critical duties with additional mitigating measures.
- The regular monitoring of blood glucose as stipulated in the protocol is essential to ensure safety.
- A traffic light system requiring action when thresholds are crossed appears to work well.
- Advances in monitoring glucose techniques has contributed to the lower rates of out-of-range readings in the ARA.MED.330 protocol over time.
- The improvements in diabetes treatments, including new insulin preparations, has contributed to the lower rates of out-of-range readings within the ARA.MED.330 protocol over time.

The practical, operational and environmental factors that impact on blood glucose management

- Pilots and ATCOs have many different working environments and occupational tasks and are unique to their specific duties.
- The integration of CGM systems hold tremendous potential for managing diabetes within the aviation industry.
- The study's focus on insulin-treated pilots' perceptions of glucose monitoring systems is a pivotal step towards addressing potential barriers and harnessing the advantages of these technologies.
- Although calibration may be required, the convenience and accuracy of CGM systems are perceived by pilots to be better than SMBG and can be further verified in real flight conditions.
- In view of the stressed and time-pressured environment that pilots and ATCOs face, this adds to its potential in improving the management of diabetes of both pilots and ATCOs in the industry.

- It should be still verified which type of operations are able to accommodate this possibility due to their occupational duties and to be confirmed that they can fly safety following the protocol requirements.

Diabetes complications

- Macrovascular complications: medical assessors should manage cardiovascular problems independent of diabetes, following MED.B.010 rules, as they do with the other flight professionals by considering that diabetes makes them more severe and paying special attention to coronary artery disease and arrhythmias.
- Microvascular complications – diabetic retinopathy: medical assessors should manage eye defects independent of diabetes, following MED.B.070 rules, as expected with people without diabetes, paying special attention to visual acuity and diplopia.
- Microvascular complications – diabetic kidney disease: medical assessors should manage renal problems independent of diabetes, following MED.B035 rules as they do with the other flight professionals by considering that diabetes makes them worsen more rapidly except for treatment regimens including kidney-protective drugs (like glifozins or GLP1-receptor agonists)
- Microvascular complications – diabetic neuropathy: medical assessors should manage neuropathy independent of diabetes, following MED.B065rules paying special attention to recurring episodes of cerebral dysfunction due to hypoglycaemia unawareness, dysesthesia, vascular dysregulation symptoms, and recurrent tachyarrhythmic episodes.

Main take-away:

- The diagnosis of diabetes is a world-wide accepted procedure but it should be emphasized that any comparison of A1C with FPG or 2-h OGTT is equivocal because resources vary between countries and a true gold standard is not available
- CGM devices that meet the ISO or FDA standards alongside occasional finger-stick monitoring for verification purposes is considered the gold standard in achieving effective glycaemic control and both pilots and ATCOs granted medical certificates to work under the ARA.MED.330 protocol would grately benefit from their use during operational tasks.
- Modern CGM systems may be useful in overcoming occupational barriers, particularly for those operating in safety-critical industries like aviation, and provide a viable alternative to SMBG.
- The ARA.MED.330 diabetes protocol, which requires regular finger-stick SMBG monitoring, is effective in enabling pilots and ATCOs with insulin treated diabetes to perform safety critical duties while maintaining good individualised glycaemic control
- The integration of CGM systems hold tremendous potential for managing diabetes within the aviation industry.
- It is possible for people with insulin-treated diabetes to perform complex safety critical occupational duties providing there is stringent compliance with a comprehensive protocol and strict oversight.

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