A real-world study of user characteristics, safety and efficacy of open-source closed-loop systems and Medtronic 670G

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Abstract
We report a real-world evaluation of the first commercially approved automated insulin delivery (AID) system, MiniMed 670G (670G), and open source-automated insulin delivery (OS-AID) systems. This was undertaken as a retrospective observational study in adults with type 1 diabetes using AID systems for 6 months or longer in a publicly funded health service using clinically validated data. Sixty-eight adults (38 670G, 30 OS-AID systems) were included. OS-AID system users were younger, had a shorter diabetes duration and a higher education status. OS-AID systems displayed a significantly better change in HbA1c (median 0.9% [IQR 0.4%, 1.1%] vs. 0.1% [IQR 0.7%, 0.2%], \( P = 0.004 \)) and time in range 3.9-10 mmol/L (mean 78.5%, SD ± 12.0% vs. 68.2% ± 14.7%, \( P = 0.024 \)) compared with 670G. Both systems showed minimal hypoglycaemia, with OS-AID systems revealing significantly improved secondary outcomes of mean glucose and percentage of time more than 10 mmol/L, with a higher percentage of time of less than 3 mmol/L. OS-AID system users displayed improved glycaemic outcomes with no clinical safety concerns compared with 670G, although higher weight-adjusted insulin dose and weight gain were noted. The study highlights key differences in OS-AID system user characteristics that are important for interpreting real-world findings from recent OS-AID system studies.

KEYWORDS
artificial pancreas systems, automated insulin delivery systems, DIY artificial pancreas systems, open-source-automated insulin delivery systems, type 1 diabetes

1 | INTRODUCTION

Hypoglycaemia and the complexity of treatment regimens remain barriers to optimal glycaemia and negatively impact quality of life in people with type 1 diabetes, resulting in few of them achieving recommended glycaemic targets.1-3 Automated insulin delivery (AID) systems utilize continuous subcutaneous insulin infusion (CSII) devices, continuous glucose monitors (CGMs) and a software controller to adapt insulin delivery in response to interstitial glucose.4 Medtronic’s MiniMed 670G (670G) represents the first commercial AID system approved for clinical use in Europe (in 2018). This system uses a proportional integral-derivative algorithm to automate basal insulin delivery to a glucose target, which cannot be set lower than 6.7 mmol/L.

The diabetes online community has driven development of open-source AID (OS-AID) systems, also known as do-it-yourself (DIY) artificial pancreas systems.5-7 Despite their unregulated status, this movement has expanded exponentially, with current estimates...
suggested over 9000 users worldwide. These systems have a variety of features that can be customized, including user-adjusted glucose targets. Published self-reported outcomes reveal clinically significant improvements in glycaemic outcomes with no safety concerns. A recent report, using largely self-reported data with clinically validated HbA1c from a large cohort using the Loop OS-AID system, provides further support for this. However, definitive randomized studies regarding the efficacy and safety of OS-AID systems have not been possible because of a lack of funding and consequent difficulties in obtaining regulatory approval. In this study, we aim to explore differences in user characteristics, clinical outcomes and safety between OS-AID systems and a commercially available closed loop system (Medtronic 670G) in a publicly funded health service using clinically validated data.

2 | RESEARCH DESIGN AND METHODS

We conducted a retrospective observational study in adults with type 1 diabetes using AID systems for 6 months or longer attending King’s Health Partner sites. This retrospective study was conducted in line with local audit protocols using existing anonymized routine clinical data accessed directly by the clinical team.

We analysed clinical data obtained from CareLink for 670G, or either Nightscout or Tidepool for OS-AID systems, recorded 6 months after AID system use for a period of 30 days. Education and socioeconomic status were determined using an Index of Multiple Deprivation (IMD) score. Percentage of time in automated mode and sensor wear time were extracted from CareLink for 670G. For OS-AID systems, percentage of time in automated mode was estimated using individual daily assessment for hour blocks when the sensor was inactive, when the system was not modulating basal, or when Nightscout logs reflected that the system was not in closed-loop mode.

The co-primary outcomes were change in HbA1c with that prior to starting AID system use (ΔHbA1c), and percentage of time in target range (TIR; 3.9–10 mmol/L). Secondary outcomes included mean glucose, standard deviation (SD), percentage of time above target range (TAR; >10 mmol/L), percentage of time below range (TBR; <3.9 mmol/L), severe hypoglycaemia (SH) and percentage of time less than 3 mmol/L, number of diabetic ketoacidosis (DKA) episodes and percentage of time less than 13.9 mmol/L. Other outcomes are listed in hierarchical order in Table 1 and Tables S1-S3. Duration of AID system use was determined from the start of the AID system until 1 April 2020.

Statistical analyses were performed using SPSS version 21 (IBM Software, Hampshire, UK). Data are reported as mean ± SD for 670G versus OS-AID systems unless stated otherwise. Median values are reported with interquartile ranges where appropriate. Statistical analyses for parametric continuous variables were performed using the two-sample Student’s t-test and, for non-parametric, non-continuous variables, were performed using a Mann–Whitney U-test. For categorical variables, differences in proportions between the groups were compared using the chi-squared test. Post hoc Bonferroni P value adjustments for multiple comparisons were made for primary, secondary and main study endpoints.

3 | RESULTS

Sixty-eight adults met the inclusion criteria (38 using 670G) (Figure S1). Demographic data are presented in Table 1. Compared with 670G, OS-AID system users were younger (40.5 ± 9.3 vs. 47.1 ± 13.4 years, P = .026), had a shorter duration of diabetes (24.6 ± 8.4 vs. 31.1 ± 13.5 years, P = .025), were predominantly male (70.0% vs. 31.6%, P = .001), and had lower baseline HbA1c (7.1% ± 1.0% [54.4 ± 10.5 mmol/mol] vs. 7.8% ± 1.2% [61.9 ± 12.9 mmol/mol], P = .012) and higher education status (8.0 vs. 6.1, P = .001), despite similar socioeconomic status scores.

Differences in CSII devices, CGM systems, algorithms and funding status are detailed in Table S1. Prior to using AID systems, all patients were on sensor-augmented pump therapy. Overall, 43.4% of OS-AID system users used out-of-warranty CSII devices, despite being eligible for NHS-funded in-warranty CSII devices. Twenty per cent of OS-AID system users used Flash glucose monitoring with unregulated near-field communication (NFC) to a Bluetooth adaptor as an alternative to real-time CGMs. Thirty per cent of OS-AID system users used OS rather than manufacturer CGM algorithms for CGM data output.

Compared with 670G, OS-AID system users had significantly improved primary glycaemic outcomes with a higher median ΔHbA1c (−0.9% [−4.2, −12 mmol/mol] vs. −0.1% [−7.3, 1.8 mmol/mol], P = .004) and higher percentage TIR (3.9–10 mmol/L) (78.5% ± 11.9% vs. 68.2% ± 14.7%, P = .024) (Figure 1). OS-AID systems revealed significantly improved secondary outcomes of mean glucose (7.6 ± 1.1 vs. 8.9 ± 1.5 mmol/L, P = .024) and percentage TAR (18.4% ± 12.1% vs. 29.21% ± 15.5%, P = .024) and percentage of time more than 13.9 mmol/L (median 2.0% [0.8%, 6.4%] vs. 5.0% [2%, 10%], P = .088). Both systems showed minimal hypoglycaemia with percentage TBR (3.2% ± 2.1% vs. 2.6% ± 4.1%, P = 1). However, a clinically non-significant but higher percentage of time less than 3 mmol/L was noted in OS-AID systems (median 0.3% [0.1%, 0.7%] vs. 0% [0%, 0%], P = .002). Contrary to this, based on clinical data during the study period, a higher observed incidence of severe hypoglycaemia (SH) was noted in 670G, which was not significant after post hoc correction (0% vs. 18.4% patients, P = .104). All SH episodes on 670G occurred outside auto-mode with a system exit of at least 2 hours prior to the event. No DKA events were noted.

Differences in device performance and dosing characteristics are presented in Table S1. OS-AID system users had significantly lower glucose targets (5.5 ± 0.5 vs. 6.7 ± 0.0 mmol/L, P < .0001), a higher percentage of time in automated mode (90.0% ± 4.6% vs. 71.6% ± 30.3%, P = .005), a higher total daily dose of insulin per kilogram (0.6 ± 0.2 vs. 0.5 ± 0.2 units/kg, P = .032), and experienced more weight gain (median weight change 1.25 [0.03, 2.78] vs. −0.3 [−2.4, 0.8] kg, P = .012) with similar carbohydrate intake. Subanalysis of 670G based on time in automated mode revealed an improved TIR for 70% or longer time in automated mode (72.1% ± 11.4% vs 70% vs. 58.6% ± 18.0% for <70%, P = .008; Table S2). Further subanalysis of OS system subtypes are detailed in Table S3, with no significant differences between them.
The results highlight improved primary glycaemic outcomes for OS-AID systems compared with 670G, despite OS-AID system users having a lower baseline HbA1c. Secondary outcomes were also in favour of OS-AID systems, except for a marginally higher risk of glucose of less than 3 mmol/L. The glycaemic outcomes reported are in line with previous observational studies for OS-AID systems and real-world data for 670G.5-8,11

The reasons for the observed differences between systems are probably multifactorial. These include lower glucose targets in OS-AID systems noted in the current study, time spent while the AID system was activated (or in automated mode), previously reported usability and human factors and prolonged time since device upload for 670G noted in the current study.12 As a first commercial system, 670G has more conservative algorithm features, and glucose targets that cannot be lowered below 6.7 mmol/L. By comparison, OS-AID

### Table 1

| TABLE 1 of baseline clinical characteristics, primary and secondary glycaemic, insulin and adverse event endpoints between 670G and OS-AID system user groups |
|-----------------------------------------------|-----------------|-----------------------------|
| **Baseline characteristics**                  | 670G (n = 38)   | OS-AID (n = 30)              |
| Age (y), mean ± SD                             | 47.1 ± 13.4     | 40.5 ± 9.3                  |
| Sex                                            |                |                             |
| Gender                                         | Male: 31.6%    | Male: 70.0%                 |
|                                              | Female: 68.4%  | Female: 30.0%               |
| Ethnicity                                      | Caucasian: 97.4%| Caucasian: 90.0%            |
|                                              | Non-Caucasian: 2.6%| Non-Caucasian: 10.0%   |
| Baseline BMI (kg/m²), mean ± SD                | 27.1 ± 5.3     | 25.1 ± 3.6                  |
| Structured education completion                | Yes: 71.1%     | Yes: 73.3%                  |
|                                              | No: 28.9%      | No: 26.7%                   |
| IMD score (socioeconomic status), mean ± SD    | 5.2 ± 2.4      | 6.1 ± 2.4                   |
| Education status, mean ± SD                    | 6.1 ± 2.4      | 8.0 ± 1.8                   |
| Duration of diabetes* (y), mean ± SD          | 31.1 ± 13.5    | 24.6 ± 8.4                  |
| Duration of AID system use† (d), median (IQR) | 226.0 (175.5-401.0) | 228.5 (152.0-585.3) |
| Baseline HbA1c, % (mmol/mol), mean ± SD        | 7.8 ± 1.2 (6.19 ± 12.9) | 7.1 ± 1.0 (54.4 ± 10.5) |
| Baseline retinopathy†                          | Moderate/severe: 31.6% No/minimal: 68.4% | Moderate/severe: 23.3% No/minimal: 76.7% |
| Baseline gastroparesis                         | Yes: 2.6%      | Yes: 0%                     |
|                                              | No: 97.4%      | No: 100%                    |
| Baseline peripheral neuropathy                 | Yes: 5.3%      | Yes: 3.3%                   |
|                                              | No: 94.7%      | No: 96.7%                   |
| Gold score, mean ± SD                         | 4.1 ± 2.0      | 3.3 ± 1.3                   |
| Baseline severe hypoglycaemia                 | Yes: 26.3%     | Yes: 10%                    |
|                                              | No: 73.7%      | No: 90%                     |
| Baseline DKA                                  | Yes: 2.6%      | Yes: 0%                     |
|                                              | No: 97.4%      | No: 100%                    |
| **Primary and secondary endpoints**           | Adjusted P     |                             |
| Change in HbA1c (%) (mean ± SD)               | −0.1 (−0.7 to −0.2) | −0.9 (−0.4 to −1.1)       |
| Change in HbA1c (mmol/mol) (mean ± SD)        | −1.0 (−7.3 to −1.8) | −9.0 (−4.0 to −12.0) |
| Mean glucose (mmol/L), mean ± SD             | 8.9 ± 1.5      | 7.6 ± 1.1                   |
| SD, mean ± SD                                 | 3.0 ± 0.7      | 2.6 ± 0.7                   |
| Severe hypoglycaemia                          | Yes: 18.4%     | Yes: 0%                     |
|                                              | No: 81.6%      | No: 100%                    |
| DKA                                           | Yes: 0%        | Yes: 0%                     |
|                                              | No: 100%       | No: 100%                    |

**Abbreviations:** AID, automated insulin delivery; BMI, body mass index; DKA, diabetic ketoacidosis; IMD, Index of Multiple Deprivation; IQR, interquartile range; OS, open source; SD, standard deviation.

*Duration of diabetes, interval from the estimated date of type 1 diabetes diagnosis to AID system commencing.
†Duration of AID system use, interval from the estimated date of starting AID system to 1 April 2020 in days.
*Baseline retinopathy was classified as Moderate/Severe = R2/R3 and No/Minimal = R0/R1 using the National Screening Committee (NSC) Diabetic Retinopathy Grading system.

*P < .05. **P < .01.

### 4 DISCUSSION

The results highlight improved primary glycaemic outcomes for OS-AID systems compared with 670G, despite OS-AID system users having a lower baseline HbA1c. Secondary outcomes were also in favour of OS-AID systems, except for a marginally higher risk of glucose of less than 3 mmol/L. The glycaemic outcomes reported are in line with previous observational studies for OS-AID systems and real-world data for 670G.5-8,11
system glucose targets can be adjusted at a lower level, as reflected in the current study. The subanalysis in the current study also highlights the impact on TIR in 670G users in those with less than 70% of time in automated mode. However, the effect of 670G on HbA1c was not clinically significant in this study and had no relationship with time in automated mode. It is possible that a higher automated mode time in 670G users may contribute to a lower TBR; however, this did not reach statistical significance in the subanalysis. The system also requires manual upload of data via a computer at home. The current study highlights the prolonged time between data uploads that requires significant user input, which may also limit optimization of variables on the systems. By comparison, OS-AID systems benefit from real-time data uploads via a smartphone. All these aspects have now been improved in the recently launched MiniMed 780G system.13 While system differences probably play an important role in the noted differences, it is also important to recognize key differences in baseline demographics. The lower age, lower duration of diabetes, higher educational status and lower baseline HbA1c in OS-AID system users may reflect their motivation to initiate systems at their own risk with community support,6-8 while additional clinical support and a Medtronic educational programme were provided for initiation of 670G systems. Nevertheless, this may translate to higher engagement, health and digital literacy in OS-AID system users, leading to better optimization of AID systems. Similarly, the higher rate of SH in 670G users, albeit when not in closed loop, may reflect access to CGMs in the UK that is limited to those with impaired awareness and recurrent SH.
Potential safety issues for OS-AID systems have been an area of concern for regulatory bodies. The current study highlights high rates of out-of-warranty CSI device use and the use of intermittently scanned CGM with unregulated algorithms. Despite this, our real-world data did not reveal any safety concerns for OS-AID systems, with similar outcomes among the main OS system subtypes. The subtle but significant increase in percentage of time less than 3 mmol/L in OS-AID systems compared with 670G is within international targets and unlikely to be of clinical concern.

OS-AID system users used more insulin despite similar reported carbohydrate intake. While this could be driven by lower targets as well as algorithm differences, it is also probably explained by unannounced carbohydrates taken by OS-AID system users for the prevention of hypoglycaemia or as unannounced meals. These effects may account for the mild, significant weight gain noted in OS-AID system users. This is an area that will require further investigation and reporting as AID systems become more widely used. Improvement in glycaemic metrics may come at the potential cost of significant weight gain. There is currently limited evidence for glycaemic benefit beyond a certain threshold of TIR. However, there may be potential for higher TIR resulting from increased insulin delivery and detrimental metabolic impact from weight gain, especially for those who are already in a higher body mass index category.

One limitation of the current study is that, as a real-world observation study, it is influenced by differences in patient characteristics, and therefore it is difficult to directly compare efficacy between the two systems. This is especially relevant when taking into consideration the different baseline characteristics noted in this study. Nevertheless, the impact of baseline characteristics and different diabetes groups on outcomes is a very relevant real-world observation that requires further understanding. It has not been possible to gain insight regarding this from largely industry-sponsored single-system studies performed in motivated individuals or insurance-driven systems where health and digital literacy may be higher. The current study would also have benefitted from detailing improvements in CGM-based glycaemic metrics. It was not possible to obtain clinically validated baseline CGM metrics, especially for Medtronic-based systems, as these systems require periodic downloads, which in most cases were only performed at clinic visits. Future versions with smartphone-based data uploads may allow improvements in CGM metrics to be detailed more precisely. While a range of predetermined time points would have been an ideal scenario, in publicly funded health systems it is difficult to obtain these measures as part of real-world observation because there are differences in attendance frequencies and impacts from missed or delayed appointments. A further limitation of the current study is that OS-AID systems may comprise different versions and branches. Users may update these and therefore it is difficult to validate precisely built versions, or any developmental branches being used.

The current study builds on a recent real-world observation in Loop OS-AID system users that used mainly self-reported data from participants who were mainly covered by private health insurance. The current study uses validated clinical data from publicly funded health systems with universal access to treatments, catering for a wide variety of demographics. It reaffirms the safety and efficacy observations noted in the Loop OS-AID study; however, it also reveals differences in key user characteristics between OS-AID systems and commercially approved systems. These have important implications because education status and age impact on both diabetes outcomes and digital literacy. With increasing AID system options available and studies focusing on single AID systems, it is important that further real-world comparisons are reported to understand differences in glycaemic outcomes and user characteristics among AID systems.

In conclusion, these clinically validated real-world data show similar efficacy with no safety concerns for OS-AID systems compared with a commercially approved AID system, and provide support for using these systems in motivated individuals displaying a high level of self-care. They also highlight key user differences between OS-AID systems and commercial AID systems that are important for interpreting real-world findings in AID system studies.

ACKNOWLEDGEMENTS
The authors would like to thank the clinical teams and participants in the study. The authors would also like to thank Prof. John Pickup for helpful comments and feedback on the manuscript. Parts of this study have been submitted in abstract form for consideration for presentation at the 14th International Conference on Advanced Technologies and Treatments for Diabetes (ATTD), Paris, France, 2-5 June 2021.

CONFLICT OF INTEREST
RJ has nothing to disclose. GG reports personal fees from Abbott Diabetes Care, Medtronic, Dexcom, Novo Nordisk, Roche and Diasend, outside the submitted work. PC reports personal fees from Abbott Diabetes Care, Medtronic, Dexcom, Insulet, Roche, Novo Nordisk, Sanofi Aventis, Lilly Diabetes and Novartis, outside the submitted work. SH reports personal fees from Novo Nordisk, outside the submitted work.

AUTHOR CONTRIBUTIONS
All authors contributed to the design of the study and interpretation of the study results. RJ, GG and SH contributed to the data collection. RJ and SH contributed to the data analysis. RJ and SH prepared the first draft of the manuscript. All authors reviewed and approved the manuscript. SH is the guarantor of the work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14439.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
REFERENCES
1. Frier BM. The incidence and impact of hypoglycemia in type 1 and type 2 diabetes. Int Diabetes Monit. 2009;21(6):210-218.
2. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. Diabetes Technol Ther. 2019;21(2):66-72.
3. NHS Digital. National Diabetes Audit, 2017-2018. Report 1: Care Processes and Treatment Targets Full Report 2019, England and Wales, 13 June 2019; 2018. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-1-care-processes-and-treatment-targets-2017-18-full-report. Accessed March 14, 2020.
4. Kowalski A. Pathway to artificial pancreas systems revisited: moving downstream. Diabetes Care. 2015;38(6):1036-1043.
5. Jennings P, Hussain S. Do-it-yourself artificial pancreas systems: a review of the emerging evidence and insights for healthcare professionals. Journal of Diabetes Science and Technology. 2020;14(5):868-877. http://dx.doi.org/10.1177/1932296819894296.
6. Melmer A, Züger T, Lewis DM, Leibrand S, Stettler C, Laimer M. Glycaemic control in individuals with type 1 diabetes using an open source artificial pancreas system (OpenAPS). Diabetes Obes Metab. 2019;21(10):2333-2337.
7. Braune K, O’Donnell S, Cleal B, et al. Real-world use of do-it-yourself artificial pancreas systems in children and adolescents with type 1 diabetes: online survey and analysis of self-reported clinical outcomes. JMIR Mhealth Uhealth. 2019;7(7):e14087.
8. Lum JW, Bailey RJ, Barnes-Lomen V, et al. A real-world prospective study of the safety and effectiveness of the loop open source automated insulin delivery system. Diabetes Technology & Therapeutics. 2021;23(5):367-375. http://doi.org/10.1089/dia.2020.0535.
9. Ministry of Housing C & LG. English indices of deprivation 2019: Postcode Lookup. http://imd-by-postcode.opendatacommunities.org/imd/2019. Accessed April 5, 2020.
10. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593-1603. https://doi.org/10.2337/dc19-0028.
11. Stone MP, Agrawal P, Chen X, et al. Retrospective analysis of 3-month real-world glucose data after the MiniMed 670G system commercial launch. Diabetes Technol Ther. 2018;20(10):689-692.
12. Lal RA, Basina M, Maahs DM, Hood K, Buckingham B, Wilson DM. One year clinical experience of the first commercial hybrid closed-loop system. Diabetes Care. 2019;42(12):2190-2196.
13. Leelarathna L, Choudhary P, Wilmot EG, et al. Hybrid closed-loop therapy: Where are we in 2021? Diabetes, Obesity and Metabolism. 2021;23(3):655-660. https://doi.org/10.1111/dom.14273.
14. Best J. DIY artificial pancreases and the dilemma of unregulated devices. BMJ. 2020;371:m3801.
15. van Deursen AJAM, van Dijk JAGM. Internet skills performance tests: Are people ready for eHealth? J Med Internet Res. 2011;13(2):e35.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Jeyaventhan R, Gallen G, Choudhary P, Hussain S. A real-world study of user characteristics, safety and efficacy of open-source closed-loop systems and Medtronic 670G. Diabetes Obes Metab. 2021;23:1989–1994. https://doi.org/10.1111/dom.14439