FEATURE ARTICLE

Continuous Glucose Monitoring Use in Clinical Trials for On-Market Diabetes Drugs

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To the best of our knowledge, there are no published data on the historical and recent use of CGM in clinical trials of pharmacological agents used in the treatment of diabetes. We analyzed 2,032 clinical trials of 40 antihyperglycemic therapies currently on the market with a study start date between 1 January 2000 and 31 December 2019. According to ClinicalTrials.gov, 119 (5.9%) of these trials used CGM. CGM usage in clinical trials has increased over time, rising from <5% before 2005 to 12.5% in 2019. However, it is still low given its inclusion in the American Diabetes Association's latest guidelines and known limitations of A1C for assessing ongoing diabetes care.

The availability of reliable continuous glucose monitoring (CGM) systems has proven to be a major innovation in diabetes management and research. Most current CGM systems are approved for 7- to 14-day use and use a wire-tipped glucose oxidase sensor inserted in subcutaneous tissue to monitor glucose concentrations in interstitial fluid. One implanted CGM system is approved for longer-term use (90–180 days); it operates with fluorescence-based technology. CGM sensors record a glucose data point every 1–15 minutes (depending on the system), collecting far more granular data and information on glycemic patterns than self-monitoring of blood glucose (SMBG) alone. Real-time CGM or intermittently scanned CGM systems send data continuously or intermittently to dedicated receivers or smartphones, whereas professional CGM systems provide retrospective data, either blinded or unblinded, for analysis and can be used to identify patterns of hypo- and hyperglycemia. Professional CGM can be helpful to evaluate patients when other CGM systems are not available to the patient or the patient prefers a blinded analysis or a shorter experience with unblinded data.

In the 20 years since CGM systems first became available to people with diabetes, technological improvements, particularly pertaining to accuracy and form factor, have made CGM increasingly viable for both patient use and clinical investigation (1,2). Average sensor MARD (mean absolute relative difference; a summary accuracy statistic) has decreased from >20 to <10% (3–10), including two systems that do not require fingerstick calibrations and three that are approved to be used for insulin dosing (11). Concurrently, size, weight, and cost of CGM systems have all decreased, while user-friendliness and convenience have increased (12).

To encourage use of CGM-derived data, researchers and clinicians have worked to develop a standard set of glycemic metrics beyond A1C. In 2017, two international groups of leading diabetes clinical and research organizations published consensus definitions for key metrics, including clinically relevant glycemic cut points for hypoglycemia (<70 and <54 mg/dL), hyperglycemia (>180 and >250 mg/dL), and time in range (TIR; 70–180 mg/dL) (13,14).

CGM-derived metrics provide far greater precision and granularity than is possible with SMBG or A1C data alone (Table 1), enabling clinicians and investigators to better represent inter- and intraday glycemic differences with metrics such as TIR, glycemic variability, and time in hypoglycemia and hyperglycemia (15). Crucially, CGM also allows for the accurate measurement and detection of nocturnal glycemia (16). The use of these metrics enables a more comprehensive understanding of glycemic management that can facilitate individualized treatment for people with diabetes or prediabetes. Although A1C

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TABLE 1 Benefits of CGM Compared With A1C Alone in Assessing Glycemia

CGM	A1C Alone
Facilitates real-time readings of blood glucose levels	Requires SMBG
Provides information on glucose variability, including duration of hypo- and hyperglycemia and nocturnal glycemia	Does not provide information on acute glycemic excursions and time in biochemical hypoglycemia and hyperglycemia
Correlates strongly with 3 months of mean glucose, TIR, and hyperglycemia metrics	Measures average glucose during the past 2–3 months
Provides information on direction of and rate of change in glucose levels	Does not provide information on direction of or rate of change in glucose levels
Provides TIR data (time spent between 70 and 180 mg/dL)	Does not have TIR measurement capability

is a useful estimate of mean glucose over the previous 2–3 months, especially when evaluating population health, it is important to include other glycemic outcomes in clinical trials. Furthermore, there is emerging evidence suggesting that TIR predicts the development of microvascular complications at least as well as A1C (17,18).

Despite recent standardization of metrics and an emerging consensus around the importance of including CGM-derived outcomes in clinical trials, to our knowledge, there has been no attempt to estimate the historical and current use of CGM in clinical trials of pharmacological agents for diabetes. We sought to analyze the use of CGM in trials of currently available pharmaceutical agents for the treatment of diabetes.

Research Design and Methods

A list of clinical trials investigating the pharmacokinetics, pharmacodynamics, safety, tolerability, and efficacy of 40 diabetes drugs currently on the U.S. market (Supplementary Appendix A) was compiled using the National Institutes of Health ClinicalTrials.gov database. Because we intentionally limited our search to trials of 40 major drugs, our approach was not intended to be representative of all clinical trials; rather, we aimed to provide broad information on the state of CGM use in diabetes clinical trials during the past 20 years. Use of CGM was determined based on the study record.

We limited our search with the following constraints: *1*) date—trial start date from 1 January 2000 to 31 December 2019, *2*) recruitment—completed; and *3*) condition/disease—diabetes. The date restriction was chosen based on U.S. Food and Drug Administration (FDA) approval of the first CGM system on 15 June 1999. We excluded any trials for which the primary outcome evaluated diabetes technology to avoid including trials investigating CGM itself with a pre- or off-market therapy used as a comparator. We also excluded trials for which interventions did not manipulate subjects' glycemia and outcomes did not evaluate drug pharmacokinetics, pharmacodynamics, safety, tolerability, or efficacy, eliminating trials for which inter- and intraday glycemic metrics would provide little value.

Using these criteria, we identified 2,032 clinical trials (Supplementary Appendix B). We plotted the proportion of trials using CGM over time and performed subgroup analyses of eight major drug classes plus pramlintide. These drug classes included basal insulins, rapid-acting insulins, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium–glucose cotransporter 2 (SGLT2) inhibitors, dipeptidyl peptidease-4 (DPP-4) inhibitors, sulfonylureas, metformin, and thiazolidinediones (TZDs). Trials investigating basal insulin/GLP-1 receptor agonist fixed ratio combination therapy were included in the whole-field analysis but were not analyzed separately given low trial count ($n = 20$).

Results

From our ClinicalTrials.gov query, we identified 2,032 clinical trials of 40 major diabetes drugs on the U.S. market, not including basal insulin/GLP-1 receptor agonist fixed ratio combination therapy. Precisely 119 (5.9%) of these trials used CGM. By drug class, CGM was used in 8.0% of basal insulin trials (55/683), 7.8% of rapid-acting insulin trials (38/486), 3.6% of GLP-1 receptor agonist trials (11/305), 4.1% of SGLT2 inhibitor trials (6/146), 1.4% of DPP-4 inhibitor trials (4/282), 8.0% of sulfonylurea trials (21/263), 3.7% of metformin trials (15/408), and 20.5% of pramlintide trials (8/39). None of the 196 TZD trials used CGM. A total of 737 trials used multiple drug classes; these were included only once in the whole-field analysis. Results are summarized in Table 2.

Clinical trials investigating diabetes drugs have increasingly used CGM as a study tool (Figure 1). The

TABLE 2 Number of Clinical Trials Starting From 2000 Through 2019 Using CGM, by Drug Class

Drug Class	Year	Trials Using CGM, *n* (%)	Total Trials, *n*
Basal insulins	Total	55 (8.0)	683
	2000–2006	10 (4.8)	209
	2007–2012	27 (8.8)	306
	2013–2019	18 (10.7)	168
Rapid-acting insulins	Total	38 (7.8)	486
	2000–2006	5 (3.0)	167
	2007–2012	19 (9.0)	211
	2013–2019	14 (13.0)	108
GLP-1 receptor agonists	Total	11 (3.6)	305
	2000–2006	1 (2.9)	35
	2007–2012	7 (4.7)	149
	2013–2019	3 (2.5)	121
SGLT2 inhibitors	Total	6 (4.1)	146
	2000–2006	0 (0)	0
	2007–2012	0 (0)	45
	2013–2019	6 (5.9)	101
DPP-4 inhibitors	Total	5 (1.8)	282
	2000–2006	0 (0)	40
	2007–2012	2 (1.3)	154
	2013–2019	3 (3.4)	88
Sulfonylureas	Total	21 (8.0)	263
	2000–2006	3 (4.0)	75
	2007–2012	9 (7.3)	124
	2013–2019	9 (14.1)	64
Metformin	Total	14 (3.4)	408
	2000–2006	0 (0)	79
	2007–2012	4 (2.0)	200
	2013–2019	10 (7.8)	129
TZDs	Total	0 (0)	196
	2000–2006	0 (0)	105
	2007–2012	0 (0)	83
	2013–2019	0 (0)	8
Pramlintide	Total	8 (20.5)	39
	2000–2006	0 (0)	17
	2007–2012	6 (35.3)	17
	2013–2019	2 (40)	5
Total	Total	119 (5.9)	2,032
	2000–2006	14 (2.7)	519
	2007–2012	51 (5.6)	913
	2013–2019	54 (9.0)	600

greatest proportion of trials with CGM occurred in 2018, when 13.2% of clinical trials ($n = 38$) included CGM as a part of the study protocol. Throughout a steady increase starting in 2004, when 2.1% of clinical trials ($n = 95$) included CGM, 2 years—2018 and 2019—had >10% CGM use in trials.

CGM use over time in trials for seven individual drug classes are depicted in Figure 2. By drug class, pramlintide clinical trials exhibited the sharpest upward trend in use of CGM. However, the number of pramlintide clinical trials ($n = 39$) was far lower than that of all other drug classes. There was only one pramlintide trial in 2013 and one in 2015, and both used CGM. Next to pramlintide, SGLT2 trials (Figure 2*D*) saw the highest proportion of CGM use in 2018, with 33.3% of trials using CGM. GLP-1 receptor agonists (Figure 2*C*) were the only analyzed class that exhibited a downward trend in CGM use. The class saw its peak CGM use in 2014, when 8.0% of clinical trials (2/25 total) used CGM.

Discussion

Developments in CGM technology in the past 20 years have allowed for the inclusion of glycemic outcomes

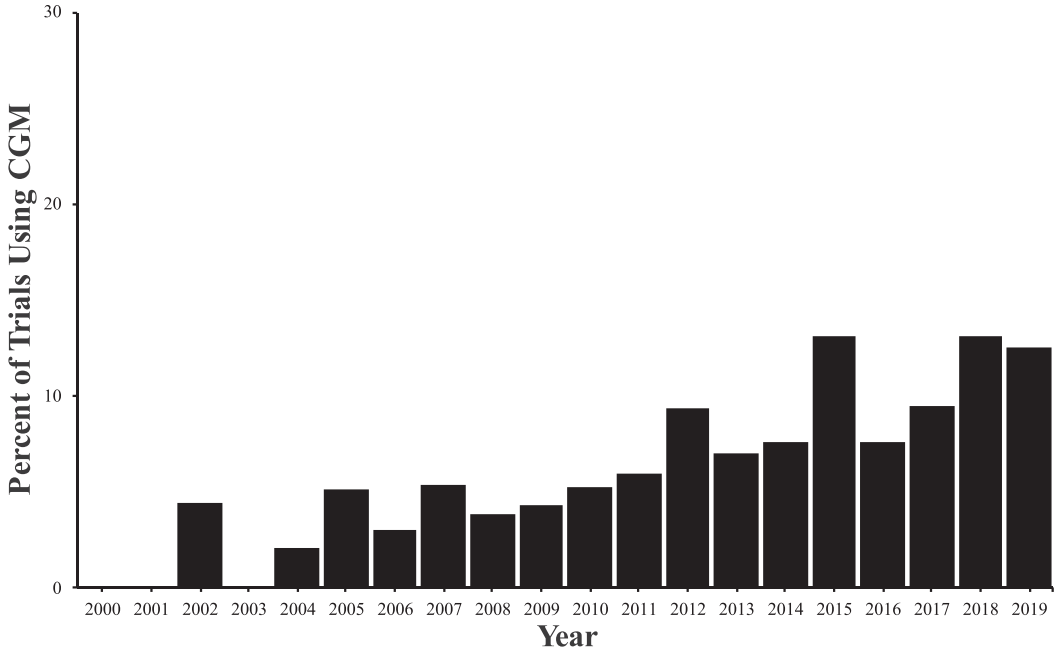

FIGURE 1 Increase over time in proportion of clinical trials using CGM across all major diabetes drug classes.

beyond A1C both in the clinic and in research, affording patients, providers, and industry a far more comprehensive view of glycemic patterns. Standardizing CGM-derived metrics and encouraging their use has been a major focus in the diabetes field during the past several years. As far as we know, no broad analysis has been conducted to review the overall implementation of CGM in pharmaceutical trials to date.

For this analysis, we looked at 2,032 studies of major diabetes drugs that were initiated after the introduction of CGM technology in 1999 to assess the degree of CGM use in clinical trials. Of the 2,032 studies, only 5.9% used CGM, although usage has increased over time from <5% before 2005 to >6% after 2011 (Figure 1), presumably as a result of increased accuracy, greater ease of use, smaller size, and decreased cost of CGM systems (12). The proportion of trials deploying CGM continues to rise, reaching >12% in 2018 and 2019.

The factors preventing greater adoption of CGM technology in trials have been well documented and include hesitation of some regulatory agencies to fully accept CGM-derived metrics as qualified end points and include CGM data in labeling. Other factors limiting widespread adoption of CGM technology include continuing education necessary for handling of devices and management of resulting data, potentially increased patient burden, and the need for consistent calibration for some of the older devices, although the latter is less of a problem with newer devices, given the availability of factory-calibrated sensors (2,19). Additional barriers include cost (for both supplies and training time) and payer unwillingness to incorporate CGM data into their policy decisions.

The most recent draft guidance from the FDA Center for Drug Evaluation and Research for glycemic outcomes in diabetes trials (released in 2008), which was withdrawn in 2020, describes A1C as "appropriate as a surrogate end point in many study designs" (20). The FDA's Center for Devices and Radiological Health has been more open to inclusion of CGM data in labeling. The European Medicines Agency recently published draft guidance endorsing CGM and patient-reported outcomes linked to CGM data in clinical investigations (21). However, none of these bodies will approve a drug or device based solely on improvement in a CGM-derived metric. Thus, there is less incentive to include CGM in clinical trials of antihyperglycemic drugs, despite an emerging consensus in support of CGM in the research and patient communities (22).

Some FDA officials have raised valid concerns surrounding the clinical relevance of CGM metrics. Currently, there exists no evidence for the long-term benefits of a given percentage of TIR that is not confounded by simultaneous A1C improvements. However, conducting a long-term randomized controlled trial to address this gap in research would be neither feasible nor ethical, representing a major barrier in convincing regulators and payers of the value of both continuous and professional CGM. However, although there has been no study indicating causality, a growing

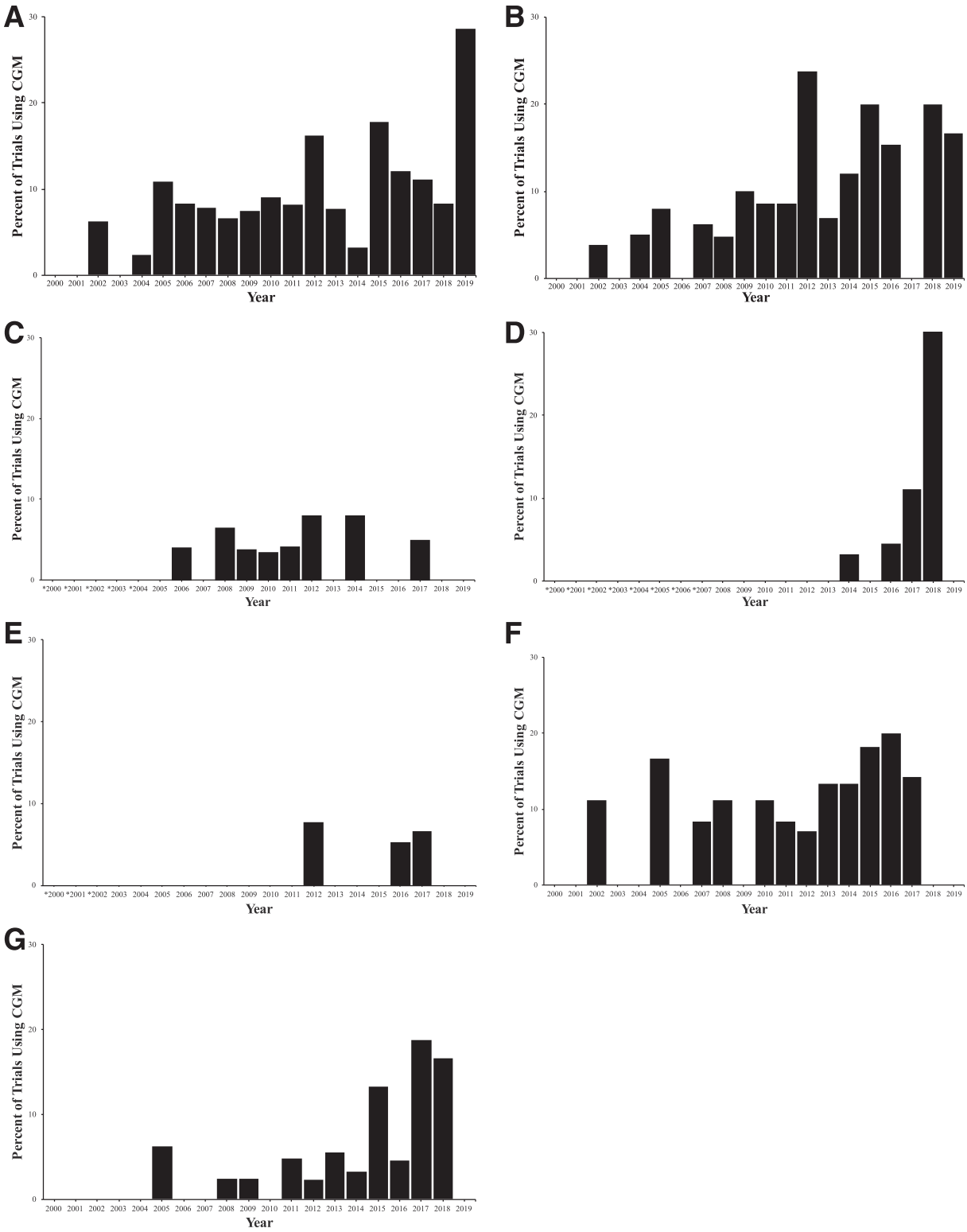

FIGURE 2 Use of CGM over time in clinical trials investigating *A*) basal insulin ($n = 683$), *B*) rapid-acting insulin ($n = 486$), *C*) GLP-1 receptor agonists ($n = 305$), *D*) SGLT2 inhibitors ($n = 146$), *E*) DPP-4 inhibitors ($n = 282$), *F*) sulfonylureas ($n = 263$), and *G*) metformin ($n = 408$). TZDs ($n = 196$) are not included here because no trials used CGM, and pramlintide is not included here because of the low trial count using this agent ($n = 39$). Asterisks preceding year numbers indicate that there were no studies of on-market drugs in that class that year; no asterisk on years with no data charted indicates that 0% of the trials that year included CGM.

body of research suggests that a lower proportion of TIR strongly correlates with higher A1C and is associated with greater risk of complications of diabetes, including retinopathy and microalbuminuria (17,18).

We are hopeful that industry, academia, and funding bodies will invest in studies to further validate CGM metrics as predictors of long-term health and quality of life in the interest of ultimately encouraging payer and regulator acceptance. In 2019, an international body of diabetes clinicians and academics gathered to determine targets for TIR, time below range, and time above range. For most people with type 1 or type 2 diabetes, the committee recommended >70% of time spent in range (70–180 mg/dL), <25% of time spent above range (>180 mg/dL), and <4% of time spent below range (<70 mg/dL) (23). Tailored recommendations for older and high-risk patients, as well as women during pregnancy and/or with gestational diabetes, were provided separately. The committee added that every 5% improvement in TIR is considered clinically meaningful. These recommendations may help to increase recognition of the value of CGM-derived metrics and ultimately drive greater use of CGM in clinical trials and practice.

This analysis includes several limitations. Primarily, there exists a lag between when trials begin and when they are posted on ClinicalTrials.gov, likely deflating the numbers of trials recorded for the most recent years. Only 38 trials were posted as beginning in 2018 and just 24 in 2019, which could result in overestimation or underestimation of the proportion of clinical trials using CGM in these later years. Further, this analysis only included trials that were indicated as "completed" on Clinicaltrials.gov. There is the possibility that more diabetes drug trials using CGM have started since 2000 but have not yet been completed or marked as such on the website. The study is also limited in that we included all clinical trials for the indicated drug classes beginning in 2000. Many of these trials' purposes are not relevant to CGM. For example, trials investigating the pharmacokinetics of a new therapy would not directly benefit from CGM, although continuous glucose data could be useful as a secondary end point. Additionally, some trial sponsors may use CGM in studies for internal purposes but not list these metrics on ClinicalTrials.gov. Finally, our data set only included studies of medications that are on the market and so excluded trials carried out as part of the clinical development of newer, pre-market therapies, which may be expected to use CGM more readily.

Given that consensus statements on definitions for CGM-derived metrics were published in December 2017, we might expect to see an uptick in CGM use in 2020 and beyond. Future studies may examine whether the consensus statements had a positive impact on use of CGM in clinical trials, based on both subsequent ClinicalTrials.gov and published literature analyses. Further subgroup analysis of the trials that do use CGM could offer additional insight into how this technology is most commonly used in a clinical trial setting.

Conclusion

CGM-derived outcomes such as TIR are increasingly valued among patients and clinicians. However, clinical trials for diabetes pharmacotherapies have been unlikely to include CGM because the value of CGM-derived outcomes has not yet been fully recognized by regulators (i.e., the FDA) or payers (i.e., insurance companies) as an indicator of safety or effectiveness. Of the 2,032 trials that we analyzed from ClinicalTrials.gov, 119 (5.9%) used CGM. CGM use in trials has increased over time, peaking in 2018 with 13.2% of trials using CGM. Given the documented limitations of A1C, the proportion of clinical trials using CGM in recent years is lower than we would have expected. We maintain that CGM should be used in all diabetes clinical trials that have glycemic end points and are hopeful that the recent consensus statements describing targets for CGM-derived outcomes will be useful in encouraging recognition of the value of CGM metrics in clinical trials. We hope that the data from our analysis will serve as a benchmark from which continued growth in CGM use in clinical trials can be measured over time.

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AUTHOR CONTRIBUTIONS

B.Q.F. and P.F.B. researched data, performed data analysis, wrote the manuscript, reviewed/edited the manuscript, and contributed to the peer-review process. A.A. researched data, performed data analysis, created tables, produced figures, and reviewed/edited the manuscript. E.F. reviewed/edited manuscript. S.F., E.M., and S.S.S. researched data, performed data analysis, wrote the manuscript, and reviewed/edited the manuscript. B.L. wrote the manuscript and reviewed/edited the manuscript. R.L.M. and M.R. researched data and reviewed/edited the manuscript. B.O. and M.S. researched data, wrote the manuscript, and reviewed/edited the manuscript. M.P. researched data. K.L.C. oversaw the study and reviewed/edited the manuscript. K.L.C. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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