Clinical Endpoints Review

Devices for Self-management of Type 1 and Insulin-Dependent type 22 Diabetes

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Objective

The objective of this report is to identify the most common therapeutic outcome domains for studies of devices used to manage type 1 (T1D) or type 2 (T2D) diabetes, identify the most commonly used individual endpoints within each domain, and compare outcomes most frequently used in clinical studies with professional recommendations. The report considers both overall outcome domains for adults with T1D and T2D and specific recommendations related to older individuals (age ≥65 years).

Overview

T1D and T2D are complex chronic conditions requiring continuous medical care. A person with diabetes produces no endogenous insulin (T1D), does not make enough insulin (T1D or T2D), or is unable to properly use insulin (T2D), a hormone produced by the pancreas. Without sufficient amounts of circulating insulin, glucose cannot enter cells, interfering with the body's ability to meet the metabolic demands of the central nervous system, muscle cells, and other tissues. T1D is believed to be an autoimmune disorder in which the body mistakenly destroys insulin-producing cells in the pancreas (ElSayed NA et al., 2023). Development of T1D is linked to family history, genetics, age, and potential environmental exposures (Rewers et al., 2018). People with T1D require lifelong insulin therapy and the condition cannot be managed with lifestyle changes. In T2D, the pancreas does not produce enough insulin and cells respond poorly to the insulin that is produced and take in less glucose. Risk factors include overweight or obesity, age ≥45 years, family history, physical inactivity, and minority race. While many people with T2D can manage their condition through lifestyle change, oral medications, or other injectable medications, the disease is progressive and the body produces less insulin over time. About 30% of patients with T2D require insulin (Basu et al., 2018).

Approximately 26.8 million U.S. adults have been diagnosed with diabetes, with nearly half (42.9%) being ≥65 years of age (CDC 2020). One in every three Medicare beneficiaries has diabetes and over 3.3 million Medicare beneficiaries use insulin (CMS, 2022). While T2D predominates, a significant number of older Americans are living with T1D as a result of improved diabetes management. Older adults are often excluded from clinical trials, which limits input for care plans for this age group. Older adults with T1D are at heightened risk for severe hypoglycemia (characterized by altered mental and/or physical status requiring assistance from another person), may have serious age-related comorbid conditions, and may have difficulty following the complex insulin regimens associated with advances in devices used to manage glycemic control (Dhaliwal et al., 2014). While episodes of severe hypoglycemia are less common among older adults with T2D, 11.5 million U.S. older adults are at risk with serious consequences including seizures, worsening cognitive function, hospitalization, and death (Laiteerapong et al., 2018).

In addition to potentially life threatening short-term complications (diabetic ketoacidosis, hyperosmolar state, iatrogenic hypoglycemic coma, hypoglycemic shock, change in mental status, metabolic derangements, etc.), diabetes has long-term macrovascular (cardiovascular disease) and microvascular (nephropathy, retinopathy, and neuropathy) complications. Diabetes is also associated with an increased risk of certain cancers (Pearson-Stuttard et al., 2021) and a heightened risk of dementia and Alzheimer's disease (Arnold et al., 2018; Biessels & Despa, 2018). Average medical costs for Americans with diagnosed diabetes (estimated at $327 billion in 2017) are 2.3 times higher than costs for those without diabetes (American Diabetes Association, 2018).

There are racial and socioeconomic disparities in the prevalence of T2D in the U.S., with rates highest among those with low educational attainment and lower incomes. Rates are lowest among non-Hispanic Whites (7.4%) and highest among Native Americans/Alaskan Natives (14.5%), Asian Indians (12.6%), non-Hispanic Blacks (12.1%), and Hispanics (11.8%) (Centers for Disease Control and Prevention, 2022). Disparities extend to diabetes treatment, with people of color and those of lower socioeconomic status having inequal access to devices used to manage diabetes (Lin et al., 2013; McAdam-Marx, 2022; Walker et al., 2021; Willi et al., 2015).

Measuring glycemic control

Glycemic control is fundamental to diabetes management and associated with a 25-50% reduction in rates of development and progression of microvascular complications (Nathan et al., 1993; UK Prospective Diabetes Study Group, 1998) and 57% reduction in risk of nonfatal myocardial infarction, stroke, or cardiovascular death (Joseph et al., 2022). Hypoglycemia is associated with an increase in arrhythmias and prolonged QT intervals (Korytkowski et al., 2017) and other markers of heightened CVD risk (Echouffo-Tcheugui et al., 2020). Glycemic control is assessed by glycated hemoglobin (A1C) measurement and calculation of glycemic variation (including incidents of hypoglycemia and hyperglycemia) obtained through continuous glucose monitoring (CGM) and blood glucose monitoring (BGM) using finger prick tests. Because A1C measures average blood glucose level over the past three months, it cannot provide a measure of glycemic variability or hypoglycemia.

International consensus on the optimal range for glycemic control is 70-180 milligrams of sugar per deciliter of blood (mg/dL) (ElSayed NA et al., 2023). Hypoglycemia is the major limiting factor in management of T1D and T2D and hospital admission rates for hypoglycemia now exceed those for hyperglycemia among older adults on Medicare (Lipska et al., 2014). Blood glucose values of 54-69 mg/dL constitute level 1 hypoglycemia. At level 2 (<54 mg/dL), neuroglycopenic symptoms (e.g., dizziness, weakness, trouble speaking, confusion) begin to occur, and immediate action is required. Level 3 hypoglycemia is a severe event characterized by altered mental and/or physical status requiring assistance from another person. On the other end of the spectrum, level I hyperglycemia is defined as blood glucose 181-250 mg/dL, while values >250 mg/dL are defined as level 2. Untreated hyperglycemia can lead to diabetic ketoacidosis, which occurs when a lack of insulin results in the body breaking down fat for fuel rather than sugar, resulting in a life-threatening buildup of ketones in the bloodstream.

There are a variety of insulin types (rapid, intermediate, or long-acting) and regimens (once daily or multiple daily injections, and insulin pump therapy) to manage blood glucose levels. An array of medical devices are available to measure and monitor glucose (blood glucose monitors, continuous glucose monitors) or dose and deliver insulin (insulin pumps, pens, syringes). More recently, diabetes technology has expanded to include automated insulin delivery systems, also known as hybrid closed-loop systems. This review will focus on three of the available devices used for the management of T1D and T2D: continuous glucose monitors, insulin pumps, and closed loop systems. While these devices are frequently associated with T1D, the approximately 30% of adults with T2D may also benefit from usage of these devices for insulin management (Daly & Hovorka, 2021).

Continuous Glucose Monitoring (CGM)

A small sensor placed below the skin measures glucose in interstitial fluid every few minutes and values are wirelessly transmitted to the monitor, either automatically or through scanning of the sensor. Sensors may be left in place for days to months, depending on the system used. Users can see their glucose levels at a glance and review changes over time to see trends. Monitors can be programmed to

sound an alarm if glucose levels are too high or low or are increasing/decreasing too rapidly; some have predictive algorithms to sound alarms if hypo/hyperglycemia is anticipated. CGM devices must typically be calibrated daily with a standard glucose meter using finger-prick blood, although some CGMs do not require calibration. The ADA recommends measuring glycemic control through A1C and time in range, while time below (<70 and <54) and above (>180) range are useful parameters for insulin dose adjustments (ElSayed NA et al., 2023). CGM devices may assist patients in reducing A1C levels and hypoglycemia for all ages in T1D (Gandhi et al., 2011) and adults with T2D (Castellana et al., 2020). The primary side effect of CGM is contact dermatitis for sensors that attach to the skin.

Continuous subcutaneous insulin infusion

Insulin pumps have been available in the U.S. for more than 40 years and provide an alternative to multiple daily injections (MDI) by releasing small doses of basal insulin continuously and/or bolus doses for corrections and timed to coincide with mealtimes, through a tube placed below the skin, to help manage blood glucose levels. Some studies comparing pump therapy to MDI have shown advantages in lowering A1C and severe hypoglycemia rates for children and adults (Layne et al., 2017; Reznik et al., 2014; Yeh et al., 2012). Some evidence indicates pump therapy may reduce diabetic ketoacidosis risk (Karges et al., 2017; Maahs et al., 2015), reduce the risk for retinopathy and peripheral neuropathy (Peters et al., 2016), and improve quality of life (Weintrob et al., 2003). Sensor-augmented pumps suspend insulin when glucose is low, which has been shown in several clinical trials to reduce nocturnal hypoglycemia in individuals with T1D (Brown et al., 2020; Forlenza et al., 2018). Side effects of pump therapy may include dislodgement or occlusion of infusion sets (with associated risks of hyperglycemia or diabetic ketoacidosis) and skin issues.

Closed-loop systems

Closed-loop systems (CLS)—also referred to as automated insulin delivery systems, bionic pancreas, and artificial pancreas—are designed to mimic physiologic insulin delivery by increasing or decreasing insulin delivery based on sensor input. CLS incorporate an insulin pump, a CGM, and an algorithm that calculates insulin delivery. Preliminary evidence from trials of various CLS suggest they may reduce A1C levels and improve time in range (Brown et al., 2019; Kaur et al., 2019; Sherr et al., 2020), lower the risk of exercise-induced hypoglycemia (Sherr et al., 2013), and have psychosocial benefits (Barnard et al., 2014; Carlson et al., 2022). Individuals still need to test their blood with a glucose meter a few times a day. Only hybrid CLS are available in the U.S. for self-management, requiring manually adjusting the amount of insulin the pump delivers at mealtimes and when a correction dose is needed. Fully closed-loop systems, which would be of particular benefit for older adults, are still in the exploratory stages.

Methods

Identifying the Literature

Searches were conducted in multiple databases and evidence-based sources to comprehensively capture prioritized outcome domains, outcome measures, and measurement instruments related to the evaluation of devices used to manage T1D or T2D in adults. Systematic searches using the terms detailed in **Appendix A** were conducted in Embase and PubMed on January 31, 2023, to retrieve prospective clinical trials, systematic reviews, and consensus statements around diabetes outcomes. Eligibility criteria are listed in **Table 1**. Staff members reviewed all articles at the title and abstract levels. Any articles possibly meeting the inclusion criteria were obtained for a full review. Individual team members reviewed all retrieved articles for inclusion.

Table 1. Eligibility Criteria for PubMed/Embase Screening

Inclusion Criteria	
#1	Reports regarding one of three medical devices used to manage type I or type II diabetes—continuous glucose monitors, insulin pumps, or closed loop systems, aka artificial pancreas—or determination of appropriate outcome measures for devices used to manage type I or type II diabetes.
#2	Paper must have either: a) Implemented a systematic search of the literature to evaluate outcomes b) Used an established process (e.g., Delphi) to arrive at consensus on outcomes Or must be one of the following study types: a) Prospective randomized controlled trial b) Prospective non-randomized study c) Prospective single-arm study
#3	Focus on patient management of diabetes in adults ≥21 years of age
#4	Minimum sample size of 25 for intervention groups in research studies and minimum study duration of 12 weeks
#5	English language publication
#6	Published on or after January 1, 2018 (5-year search)
Exclusion Criteria	
#1	Reports on a drug, biologic, behavioral, or other non-medical device intervention to manage type I or type II diabetes; reports regarding devices outside the scope of this review (insulin pens and syringes, glucose meters)
#2	Focused on an indication other than type I or type II diabetes (such as gestational diabetes)
#3	Not one of the included study types listed in Inclusion Criteria #2, such as: a) Commentary, opinion, or editorial b) Narrative reviews, conference abstracts, or protocols c) Case report/case series, cross-sectional, or case-control studies d) Retrospective studies e) Prospective observational studies
#4	Does not discuss or report on outcome measures used to evaluate devices for management of type I or type II diabetes
#5	Does not focus on patient management of diabetes (i.e., focuses on clinical management in a surgical or inpatient setting, focuses on clinician decision-making)
#6	Focuses on an exclusively pediatric population
#7	Non-English language publication
#8	Published prior to January 1, 2018

Targeted searches for interventional clinical trials were performed on clinicaltrials.gov to augment the PubMed/Embase searches and provide additional information on prioritization of primary and secondary outcomes in evaluating devices used to manage diabetes. Details of these scans are documented in **Appendix A**. Supplementary scans were also completed within the following sources for grey literature relevant to the project scope to identify recommendations and consensus related to outcomes in studies pertaining to efficacy of devices used for self-management of T1D and T2D: Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness reviews, Cochrane Library, and Food and Drug Administration (FDA) guidance documents. Searches of professional societies included the American Diabetes Association, American Association of Clinical Endocrinology, and the Endocrine Society.

Data Abstraction and Data Management

Consensus statements from professional societies were reviewed to extract recommendations for research and prioritized outcomes for comparison with the range of outcome measures reported in clinical studies of safety and effectiveness of devices used to manage T1D and T2D, including any recommendations pertaining specifically to older patients. Data regarding prioritized outcomes, discussion of primary versus secondary outcomes, and tools referenced regarding qualitative metrics

were extracted from systematic reviews. Data on outcomes used in clinical trials and prospective interventional studies to assess efficacy of insulin pumps, CGMs, and CLSs in self-management of diabetes were extracted from PubMed and Embase publications and clinicaltrials.gov records. Extracted data included country, study design, clinical focus (T1D, T2D, or both), age group of study subjects (adult (≥18 years), senior (≥65 years), or combined pediatric/adult), sample size, duration of intervention, device used by intervention group, treatment of control group (if any), the first five primary outcomes listed, the first five clinical secondary outcomes listed, the first five qualitative secondary outcomes listed (if any), and safety outcomes. Where qualitative measures were included, information on survey instruments was extracted. A flag was created to identify studies that enrolled older adults. While inclusion criteria specify an age range for enrollment, not all articles provided detail on the age ranges of actual subjects enrolled.

Data were coded and cross-referenced between the spreadsheet containing data from published articles and the spreadsheet with clinicaltrials.gov data to ensure consistency and uniformity of categorizations and coding. Composite outcomes (e.g., time above/below range) were separated into their parts. Data were checked for accuracy and completeness, and any missing or suspect values were verified. The two spreadsheets were then compared for duplicates. Where data on the same study was available from both a published article and a clinicaltrials.gov record, the published article was retained for analysis, and the clinicaltrials.gov record was omitted, on the reasoning that a published article provides a more precise record of how the research was actually conducted, as opposed to what researchers initially planned. Data extracted from published articles were then combined with data extracted from clinicaltrials.gov to create a dataset for analysis. The coded data were input into SAS 9.4 (SAS Institute Inc., Cary, NC) for analysis.

Data Analysis

For data abstracted from the research studies that met inclusion criteria, descriptive statistics were run for overall clinical outcomes, the subsets of primary and secondary clinical outcomes, and the subset of studies that enrolled older adults. Descriptive statistics were also obtained for safety and qualitative outcomes. Crosstabs and Fisher's exact tests were run to identify any differences in outcome measures by device type, diabetes type (T1D, T2D), and studies that did or did not enroll older adults, while t-tests were used to explore differences in continuous variables (enrollment numbers, study duration).

The data were synthesized to create a prioritized list of outcomes and instruments that also included commonly used endpoints and instrument parameters. In consultation with CMS, an outcome was considered prioritized if it was ≥ the 50th percentile after ranking by citation volume. Prioritized outcomes were organized into domains in keeping with the standardized outcome classification system developed for the Core Outcome Measures in Effectiveness Trials (COMET) database (Dodd et al., 2018). Of note, per the COMET taxonomy, specifically named adverse events (i.e., severe hypoglycemia) are categorized under the appropriate taxonomy domain (i.e., physiological/clinical), rather than within the adverse event domain. Citation volumes for instruments used in patient-reported outcome measures were also collected and specific instruments were deemed prioritized if they were ≥ the 50th percentile after ranking by citation volume.

Details for prioritized instruments used in patient-reported outcomes were synthesized and tabulated (**Appendix B**), capturing additional information obtained through targeted literature searches on reliability, validity, and clinically meaningful differences (i.e., minimal clinically important differences

(MCID) and minimal important differences (MID)), where possible. Furthermore, instrument-specific characteristics that could potentially contribute to decision-making during stakeholder discussions were captured, such as number of items, scoring rubric, dimensions assessed, and intent of development.

Quality Assessments

It was not necessary to assess the methodological quality of the included clinical trials because the objective of this report is to identify the most common therapeutic outcome domains for studies of devices used to manage T1D or T2D, identify the most commonly used individual endpoints within each domain, and compare outcomes most frequently used in clinical studies with professional recommendations.

Results

Literature

Using the search terms in **Appendix A** within the PubMed and Embase databases, we retrieved 6,062 records. After deduplication, 4,333 records were screened at the title/abstract level and 116 were included for full-text screening. After full-text articles for these records were obtained and screened, 52 papers met the eligibility criteria for this review, including 48 research studies and 4 systematic reviews. Of the 64 excluded full-text articles, the majority were excluded due to study design (30%), focus on a pediatric population (22%), not meeting minimum requirements for sample size or study duration (16%), or excluded publication type (9%). Additional details are provided in **Appendix G1**.

Searches in clinicaltrials.gov for studies published from 2018 onwards related to devices for management of T1D or T2D yielded 485 results. Following the removal of duplicates and screening of trial summary data to exclude studies related to behavioral interventions, drug evaluations, decision support tools, pediatric populations, or gestational diabetes, 114 relevant studies remained. Full records were reviewed for all 114 clinical trials, leading to exclusion of 82 records that failed to meet inclusion criteria for sample size or study duration, were limited to a pediatric population, or did not focus on one of the three devices of interest (instead evaluating the performance of software or an algorithm, for example). Of the 32 trials that met inclusion criteria, 21 trials were not represented in the literature search. Additional details are provided in **Appendix G2**.

The 48 published research studies and 21 clinical trials were combined for analysis. As a result, data synthesis includes information from 69 studies. No relevant reviews from AHRQ or Cochrane Reviews published after January 1, 2018, were located. Four relevant systematic reviews were identified, as well as six consensus statements from research groups or professional societies.

Professional Consensus on Recommended Outcome Measures

Six clinical consensus statements were identified, including one that specifically addressed treatment of diabetes in older adults (LeRoith et al., 2019). The analysis included one consensus statement just outside the 5-year time frame because it directly addressed outcome measures for clinical trials (Agiostratidou et al., 2017). Homogeneity across recommendations was strong, and most were drafted or endorsed by the same core set of organizations, including the American Diabetes Association and American Association of Clinical Endocrinology. Two consensus statements focused specifically on CGM (Battelino et al., 2023; Battelino et al., 2019), one focused on CGM and pumps (LeRoith et al., 2019), and the remainder addressed all three devices under review (CGM, CLS, pumps). Five of six consensus statements addressed both T1D and T2D, while one statement (Agiostratidou et al., 2017) addressed clinically meaningful outcome measures for children and adults with T1D.

All six consensus statements addressed limitations of A1C for measuring glucose variability, noting that A1C cannot capture fluctuations in glucose levels and is not reflective of patients' day-to-day experience, but all acknowledged A1C as the standard outcome measure for assessing glycemic control. Two statements (Battelino et al., 2019; Agiostratidou et al., 2017) were specifically focused on standardizing clinically meaningful outcome measures beyond A1C. Nonetheless, all six consensus statements included A1C as a recommended outcome measure. As seen in **Table 2**, A1C and hypoglycemia (<70 and <54 mg/dL) were universally recommended outcome measures. Time in range (70-180 mg/dL) and time above range (>250 mg/dL) were additional recommended outcome measures in five of six consensus statements. The ADA Standards of Care 2023 advise that time in range is associated with the risk of microvascular complications and can be used for assessment of glycemic control, combined with measures of time below range and time above range. Simplified diabetes management strategies are advised for patients ≥65 years with limited life expectancy or where harms of treatment outweigh the benefits.

In 2019, the Endocrine Society issued clinical practice guidelines for treatment of diabetes in older adults. Cosponsors included the European Society of Endocrinology, the Gerontological Society of America, and the Obesity Society. The guidelines addressed glycemic control in both T1D and T2D. While A1C is acknowledged as the gold standard to measure treatment efficacy and predict the risk of long-term complications, the authors advise that A1C can have limited accuracy in the older adult population as a result of disorders such as red blood cell turnover, anemia, and chronic kidney disease, which affect A1C levels. This issue is also addressed in the ADA's discussion of glycemic control in the senior population (ADA, 2023). The recently released FDA guidance for industry (FDA, 2023) also advises that factors that affect red blood cell turnover may result in a falsely low or high A1C and adversely affect interpretation of the clinical study effectiveness measure. As a result, they advise that subjects with anemia or recent blood transfusion should be excluded in study protocols.

The 2021 recommendations from the American Association of Clinical Endocrinology (Grunburger et al., 2021) note the limitations of A1C for making therapeutic decisions and suggest preference be given to mean glucose, percent time hypoglycemic, time in target range, and percent time hyperglycemic in decision making, although A1C is still listed as a primary outcome measure. The ADA Standards of Care 2023 recommend that A1C not be used in older adults with very complex health conditions; care should instead focus on avoiding hypoglycemia and symptomatic hyperglycemia. The recommendation encompasses older adults in long-term care facilities and those with end-stage chronic illness, moderate-to-severe cognitive impairment, or two or more impairments to activities of daily living. The ADA recommends that CGM be used for older adults with T1D and suggests it be used for those with T2D to better capture glucose variability.

Additionally, draft guidance released by the US Food and Drug Administration in May 2023 regarding efficacy endpoints for diabetes drugs discusses recommended metrics for assessing glycemic control in clinical trials. Reduction in HbA1c continues to be recommended as a validated surrogate endpoint for microvascular risk reduction (FDA, 2023), although the FDA also announced that it is considering a reduction in the risk of hypoglycemia to be a clinically relevant outcome measure for clinical trials alongside a reduction in or maintenance of an acceptable A1C value. The ADA recommends a combination of A1C and measures of glycemic variability (particularly measures of hypoglycemia for older adults) in the management of patients with T1D or T2D on insulin therapy (ElSayed NA et al., 2023).

Table 2. Outcome measures recommended in professional society consensus statements

Lead organization	Advanced Technologies & Treatments for Diabetes Congress (Battelino et al., 2019)	American Assn of Clinical Endocrinology (Battelino et al., 2023)	American Assn of Clinical Endocrinology (Grunburger et al., 2021)	American Assn of Clinical Endocrinology (Agiostratidou et al., 2017)	American Diabetes Association (ADA, 2023)	Endocrine Society (treatment of diabetes in older adults) (LeRoith et al, 2019)
diabetes type	T1D, T2D	T1D, T2D	T1D, T2D	T1D	T1D, T2D	T1D, T2D
issues related to older adults	adjusted target metrics	adjusted target metrics	adjusted target metrics	addresses issues related to older adults, does not provide target metrics	addresses issues related to older adults, does not provide target metrics	recommends focus on hypoglycemia, not A1C, for medically complex patients
device(s)	CGM	CGM	CGM, CLS, pumps	CGM, CLS, pumps	CGM, CLS, pumps	CGM, pumps
purpose of statement	CR and CP	CR	CP	CR	CP	CP
A1C	•	•	•	•	•	•
time in range	•	•	•	•	•	
hypoglycemia (<70 mg/dL)	•	•	•	•	•	•
level 2 hypoglycemia (<54 mg/dL)	•	•	•	•	•	•
hyperglycemia (>180 mg/dL)	•	•	•	•		
level 2 hyperglycemia (>250 mg/dL)	•	•	•	•	•	
time in diabetic ketoacidosis				•		
mean glucose						
coefficient of variation		•				
patient-reported outcomes		•		•		

Abbreviations: A1C: glycated hemoglobin HbA1c; CGM: continuous glucose monitor; CLS: closed loop system; CP: clinical practice; CR: clinical research

Minimal Clinically Important Difference (MCID)

A 2019 systematic review was unable to identify any studies that had attempted to identify MCID in glycemic control outcomes (Hamersky et al., 2019). Based on ADA (ADA, 2009) and UK National Institute for Health and Clinical Excellence treatment guidelines (National Institute for Health and Care Excellence, 2015), change in A1C value of ≥0.5% is accepted as clinically significant. Professional recommendations that provided goals for assessment of efficacy of glycemic control measures available through CGM were in agreement regarding outcome goals, with several (ADA, 2023; Battelino et al., 2019; Grunburger et al., 2021) providing specific outcome goals for the senior population, as seen in **Table 3**. MCID are established for some of the prioritized qualitative measures used in studies related to devices used to self-manage T1D and T2D, as described in **Appendix B**.

Table 3. Target metrics for adults with T1D or T2D, defined by international professional consensus statements (Battelino et al., 2019; Grunburger et al., 2012; Battelino et al., 2023 ADA, 2023)

outcome measure	goal for adults	goal for older adults (age ≥65 years)
A1C	<7% or individualized	<7.0-<7.5% in healthy older adults, <8% in complex intermediate, do not use in very complex (focus on hypoglycemia)*
time in range	>70%	>50%
level 1 hypoglycemia (<70 mg/dL0	<4%	<1%
level 2 hypoglycemia (<54 mg/dL)	<1%	~0% (a difficult target to meet without assistance of a device)
level 1 hyperglycemia (>180 mg/dL)	<25%	<10%
level 2 hyperglycemia (>250 mg/dL)	<5%	<10%

* complex/intermediate: multiple coexisting chronic illnesses and either two or more impairments in instrumental activities of daily living (managing medication, preparing meals, etc.) or mild-to-moderate cognitive impairment; very complex/poor health: long-term care or end-state chronic illness or moderate-to-severe cognitive impairment or two or more impairments in activities of daily living (bathing, dressing, eating, etc.)

Overview of Articles and Clinical Trial Included in Data Synthesis

The analyzed data set contained 48 published articles and 21 clinicaltrial.gov records, for 69 studies analyzed. Randomized Controlled Trials (RCTs) predominated (54%), followed by prospective single-arm studies (29%), randomized or nonrandomized crossover trials (13%), and non-randomized trials (4%). Although most individuals with diabetes have T2D, the majority of studies were related to T1D (69.6%), compared to studies that focused on T2D (18.8%) or both types (11.6%).

Mean age for the 48 published studies ranged from 12-69 years (the clinicaltrials.gov records included plans for enrollment, but no details on numbers subsequently enrolled). Mean study duration was 5.3 months (standard deviation (SD) 2.3), with a range from 3-12 months. Minimum sample size for inclusion in the evidence synthesis was 25 in the intervention group. Across the 48 published studies, the mean sample size was 142 (SD 84.03, range 25-420). Average enrollment did not differ for device type (p=0.8571), diabetes type (p=0.8571), or enrollment of older adults (p=0.1589). Study duration did not differ for device type (p=0.760), diabetes type (p=0.4307), or enrollment of older adults (p=0.9572).

Thirty-one of 69 studies (45%) were conducted in the U.S., while 32 (46%) were outside of the U.S. and 6 (9%) had study sites both inside and outside the U.S. One entry in clinicaltrials.gov, an industry-sponsored study, did not specify the location of study sites. Results of studies conducted outside the U.S. may not be generalizable to Medicare beneficiaries due to differences in factors affecting management and outcomes for people with diabetes, such as diet, heterogeneity of ethnicity/race, access to healthcare and medications, etc.

CGM was the device type studied most frequently (51% of studies), while 35% (24) of studies focused on CLS, and 14% (10) on insulin pumps. Studies related to T1D primarily focused on CLS (47.9%) or CGM (37.5%), while a minority focused on insulin pumps (14.6%). There was no difference in focus by age group (p=0.9593), with the majority of all T1D studies focused on CLS across all age groups: mixed pediatric and adult, adult (age ≥18 years), or older adult (age ≥60 years) only. Studies limited to T2D almost exclusively concentrated on CGM (85%), with only 2 of 13 studies focused on insulin pumps and none on CLS.

Inclusion of Older Adults in Research

As seen in **table 4**, 26 of 48 published articles (54%) enrolled older adults (age ≥60 years), while 13 (27%) did not enroll any older adults. Nine articles (19%) did not provide sufficient detail to determine whether older adults had been enrolled. Mean age for the 26 studies ranged from 28-69 years. Mean study duration was 5.0 months (SD 2.2). The majority of the 26 studies focused on T1D (61.5%). Seven studies focused on T2D (26.9%) and 3 (11.5%) included both T1D and T2D. RCTs predominated (57.7%), followed by prospective single arm trials (26.9%). Three articles described crossover trials (11.5%) and 1 described a non-randomized trial (3.8%). CGM was the most frequently studied device (46.2%), followed by CLS (38.5%), and insulin pumps (15.4%). Nineteen entries in clinicaltrials.gov (90.5%) reported the senior age group fell within inclusion criteria. However, with the exception of one trial that focused solely on adults ≥65 years of age, it was unknown if or how many older adults would actually be enrolled.

For the subset of 42 studies (3 trials and 39 published articles) where it was clear whether older adults were or were not enrolled, there was no significant difference between T1D and T2D studies in likelihood of enrolling older adults (p=0.1081). Device type did not differ for studies that did or did not include older adults (p=0.666). Studies conducted solely in the US (83.3%) were more likely than those conducted solely outside of the US (47.6%) to include older adults (p=0.0428).

Table 4. Enrollment of older adults (age ≥60 years) in included studies

		trials (n=21)	published studies (n=48)	total
inclusion criteria	older adults included	19	38	57
	older adults excluded	2	10	12
actual enrollment	enrolled older adults	1 (limited to older adults)	26 (2 limited to older adults)	27
	did not enroll older adults	2	13	15
	enrollment of older adults unknown	18	9	27

Studies Limited to Older Adults

There is a paucity of studies that focused solely on older adults: two published articles (Boughton et al., 2022; Pratley, et al., 2022) and one clinical trial record (NCT04016662). None of these studies focused on T2D, which is far more common among older adults (Laiteerapong et al., 2011). All three studies focused on T1D: two crossover trials testing efficacy of CLS and one RCT exploring CGM. Study duration for the two published articles ranged from 4-6 months. Mean enrollment ranged from 37 to 203.

The ongoing trial, Automated Insulin Delivery in Elderly With Type 1 Diabetes (AIDE T1D) (NCT04016662), is designed to test the benefits of closed loop systems for reducing hypoglycemia in adults $\geq$65 year of age and has an estimated completion date of December 2023. The authors note that clinical trials of automated insulin delivery technologies have not included older adults in sufficient numbers to identify ways in which efficacy and quality of life impacts may differ from those observed in younger age groups. They argue that primary endpoints of studies with younger populations have focused on reducing hyperglycemia, while avoidance of hypoglycemia is the primary concern for older adults with T1D, as the altered mental status associated with hypoglycemia places older adults at increased risk for falls, car accidents, emergency room usage, and hospitalizations. The multi-center U.S. study utilizes a randomized crossover trial design, consisting of three sequential 12-week periods, with the hybrid closed loop feature used during one period, the predictive low glucose suspend feature used during one period, and sensor-augmented insulin pump therapy (control) during one period. After the last crossover period, participants will be given the opportunity to use study devices for an additional 12 weeks to assess preference of system use and associated characteristics, durability, and safety in a more real-world setting with less frequent study contact. Estimated enrollment is 90. The primary outcome is percent time in hypoglycemia (<70 mg/dL), while secondary outcomes include percent time in level 2 hypoglycemia (<54 mg/dL), frequency of hypoglycemia, mean glucose, percentage of time in range, coefficient of variation, A1C, percent time in hyperglycemia (>180, >250), and hypoglycemia unawareness as measured through the Gold survey. Additional survey-based measures include the Hypoglycemia Fear Survey, Diabetes Distress Scale, AIDE Technology Acceptance questionnaire, and rating of system usability.

Defining Most Commonly Reported Outcome Measures

An outcome was considered prioritized if it was $\geq$ the 50th percentile after ranking by citation volume (a metric established in consultation with CMS), and prioritized outcomes were organized into domains. In keeping with the standardized outcome classification system developed for the Core Outcome Measures in Effectiveness Trials (COMET) database (Dodd et al., 2018), specifically named adverse events (i.e., severe hypoglycemia) are categorized under the appropriate taxonomy domain (i.e., physiological/clinical), rather than within the adverse event domain.

Primary and Secondary Clinical Outcomes

Time in range (71.0%), level 1 hypoglycemia (<70 mg/dL) (62.3%), A1C (50.7%), and level 1 hyperglycemia (>180 mg/dL) (49%) were the prioritized outcome measures, while time in range (40.6%) and A1C (34.8%) were the most frequently utilized primary outcome measures. For studies enrolling older adults, time in range (37.0%), HbA1c (33.3%), and level 1 hypoglycemia (22.2%) were the most frequent primary outcomes, while time in range (81.5%), level 1 hypoglycemia (77.8%), level 1 hyperglycemia (63.0%), A1C (55.6%), and level 3 hypoglycemia (55.6%) were the most common overall outcome measures. For the three studies limited to older adults, two used level 1 hypoglycemia as the primary outcome measure and one used time in range. A1C was not used as a primary or secondary

outcome in any of the three studies limited to older adults. The complete list of prioritized outcome measures in the identified studies is detailed in **Appendix Table B1**, while the complete list of prioritized outcome measures for studies involving older adults is detailed in **Appendix Table B2**.

Exploring differences in outcome measures by diabetes type (limited to 61 cases that were T1D or T2D and excluding 8 studies that included both types of diabetes), only level 2 hypoglycemia (<54 mg/dL) was found to be a more commonly used outcome measure in T1D studies (39.6%) than in T2D studies (7.7%) (p=0.044). Outcome measures utilized differed significantly for different device types (n=69). CLS studies (92%) were more likely than studies of pumps (70%) or CGM (57%) to include time in range as an outcome measure (p=0.0113). There were no differences by device type in likelihood of including level 1 hypoglycemia as an outcome (p=0.0636) or primary outcome (p=0.4450), but CLS studies were more likely than pump or CGM studies to use level 2 (p=0.0185) or level 3 (p=0.0141) hypoglycemia as outcomes. Both mean glucose (p=0.0087) and diabetic ketoacidosis (p=0.0100) were also significantly more likely to be used as outcomes in studies of CLS. Studies for all three device types were equally likely to incorporate A1C as an outcome measure (p=0.532) or primary outcome measure (p=0.7811).

Time in range was the only outcome measure which was utilized more frequently in studies that enrolled older adults (81.5%) than in studies that did not (40.0%) (p=0.0148). Measures of hypoglycemia (any level) were not

more frequently included in studies enrolling older adults. At least one measure of hypoglycemia was incorporated as an outcome measure in 96.3% of studies enrolling older adults, compared to 86.7% of studies that did not enroll older adults (p=0.2866). Likewise, measures of hyperglycemia (any level) were not more frequently included in studies enrolling older adults. At least one measure of hyperglycemia was included as an outcome measure in 46.7% of studies enrolling older adults and 66.7% of studies that did not enroll older adults (p=0.3256).

Alignment with International Consensus Statements

All six professional consensus recommendations identified A1C and level 1 (<70 mg/dL) and level 2 (<54 mg/dL) hypoglycemia as preferred outcome metrics. Five of six also included usage of time in range and level 2 (>250 mg/dL) hyperglycemia as additional preferred outcome measures.

Only 4 of the 69 studies reviewed (5.8%) included A1C, level 1 hypoglycemia, and level 2 hypoglycemia as outcome measures; all 4 were studies of CLS (**table 5**). However, 30 studies (43.5%) included A1C and at least one measure of hypoglycemia. There were no significant differences in likelihood of including A1C and at least one measure of hypoglycemia as outcome measures by diabetes type, device type, or enrollment of older adults. Twenty-one studies (30.4%) included A1C, at least one measure of hypoglycemia, and time in range as outcome measures, with no differences by diabetes type or device type. Studies enrolling older adults (44.4%) were more likely than studies that did not enroll older adults (13.33%) to include A1C, time in range, and any measure of hypoglycemia as outcome measures (p=0.0493). Fourteen studies (20.3%) included A1C, time in range, and a measure of both hypoglycemia and hyperglycemia, with no differences by diabetes type, device type, or enrollment of older adults.

Table 5. Alignment of outcomes identified in 69 research studies with international professional consensus statements, n (%)

combination of outcome measures		included A1C, level 1 hypoglycemia, and level 2 hypoglycemia	included A1C and any measure of hypoglycemia	included A1C, time in range, and any measure of hypoglycemia	included A1C, time in range, any measure of hypoglycemia, and any measure of hyperglycemia
all (n=69)		4 (5.80)	30 (43.48)	21 (30.43)	14 (20.29)
diabetes type (n=61)	T1D (n=48)	4 (8.33)	23 (47.92)	17 (35.42)	10 (20.83)
	T2D (n=13)	0	6 (46.15)	3 (23.08)	3 (23.08)
	p	0.5691	1	0.5159	1
device type (n=69)	CGM (n=35)	0	17 (48.57)	10 (28.57)	8 (22.86)
	pump (n=10)	0	4 (40.00)	3 (30.00)	1 (10.00)
	CLS (n=24)	4 (16.67)	9 (37.50)	8 (33.33)	5 (20.83)
	p	**0.0207**	0.7125	0.9358	0.8440
enrolled older adults (n=42)*	no (n=15)	1 (6.67)	7 (46.67)	2 (13.33)	2 (13.33)
	yes (n=27)	3 (11.11)	15 (55.56)	12 (44.44)	8 (29.63)
	p	1	0.7488	**0.0493**	0.2860

*tests excluded 27 studies where enrollment of older adults was unknown

Safety Outcomes

Severe hypoglycemic events (39%) were the most frequently reported safety outcome, reported in 27 of 69 studies, followed by diabetic ketoacidosis (33%). No studies were halted due to adverse events. In **Appendix Tables B1 and B2**, these measures are reported in the physiological/clinical domain, rather than the adverse event domain, in keeping with the standardized outcome classification system developed for the Core Outcome Measures in Effectiveness Trials (COMET) database (Dodd et al., 2018). Twenty studies (29%) included serious adverse events as a safety outcome, 17 included adverse events (25%), 11 included drug-related adverse events (16%), 3 included procedure-related adverse events (4%), 3 included hospitalization (4%), and 1 included adverse drug events (1%). Nineteen studies (27.5%) did not include discussion of specific safety outcomes.

Patient Reported Outcomes

Patient-reported measures were additional prioritized outcomes identified in the 2017 multi-agency consensus statement on assessment of glycemic control in individuals utilizing technologies for self-management of T1D and T2D (Agiostratidou et al., 2017). Only 2 of the 69 studies included a patient-reported measure as a primary outcome, but 40 of the 69 studies (58%) incorporated at least one patient-reported measure as a secondary outcome, with no statistically significant difference by device type (p=0.1960) or diabetes type (0.7552).

None of the studies enrolling older adults included patient-reported measures as a primary outcome, while 13or (48%) included them as secondary outcomes. There was no statistically significant difference in likelihood of including patient-reported outcomes in studies that enrolled older adults and studies that did not (p=0.1930). For the 27 studies that enrolled older adults, there was no difference in likelihood of including patient-reported outcomes in studies that focused on T1D and those that focused on T2D (p=0.7084), but studies focused on CGM (76%) were more likely than those focused on pumps

(40%) or CLS (37.5%) to include patient-reported outcomes (p=0.0446). The Diabetes Distress Scale, Diabetes Treatment Satisfaction Questionnaire, Hypoglycemia Fear Survey, and Problem Areas in Diabetes questionnaire were the most commonly utilized survey instruments. **Appendix Table B3** describes frequencies, psychometric properties, and MCID where known.

Systematic Reviews

Four systematic reviews were identified that met the inclusion criteria. SRs differed in their purpose and goals, as described below, but all were limited to studies with a minimum duration of 12 weeks. Two systematic reviews focused on adults with T2D (Decembrini et al., 2019; Ida et al., 2019), while two focused on children or adults with T1D (Dicembrini et al., 2021; Zeng et al., 2022). All four combined systematic reviews with meta-analysis; as a result, all reflect the prioritization of outcome measures by the systematic review team rather than reporting on all primary and secondary outcomes in included studies. Dicembrini et al. (2019) focused on T2D and included 12 studies in their SR; they did not define age ranges or any inclusion/exclusion criteria related to age. Ida et al. (2019) also focused on T2D and mean age for all seven studies included was >55 years. Both Zeng (2022) and Dicembrini (2021) focused on T1D and included both adult and pediatric studies; the former included 17 randomized crossover trial and the latter included 25 trials. None of the four systematic reviews included any discussion of issues specific to older adults, limiting guidance for device manufacturers on key outcome domains for members of this population.

Table 6 describes the level of agreement between the outcome measures prioritized in professional society consensus statements and the outcomes of interest in each systematic review. The critical primary outcomes identified in professional consensus statements—A1C and hypoglycemia—were included as outcomes in three of the four systematic reviews (75%). A1C and severe hypoglycemia (an event characterized by altered mental and physical status requiring the assistance of another person) were the most commonly used outcome metrics. Patient-reported outcomes were addressed in 50% of systematic reviews, including both SRs focused on T2D.

Table 6. Inclusion of outcomes prioritized in professional consensus statements in systematic reviews/meta-analyses

Lead author, Year	Diabetes type	A1C	Time in Range	Time below Range	Time above Range	Severe Hypoglycemia*
Zeng, 2022	T1D		●	●	●	●
Dicembrini, 2021	T1D	●	●			●
Ida, 2019	T2D	●		●		
Dicembrini, 2019	T2D	●		●		●

* An event characterized by altered mental and physical status requiring assistance of another person or hospitalization, as defined in individuals SRs

Abbreviations: A1C: glycated hemoglobin HbA1c

A group of Chinese researchers published a 2022 meta-analysis that explored CLS in children and adults with T1D (Zeng et al., 2022), including 17 randomized crossover trials (438 subjects) that compared CLS to insulin pumps, with or without predictive low glucose suspend systems. The primary outcome of interest was the percent time in target range (70-180 mg/dL). Secondary outcomes included time in hypoglycemia (<70 mg/dL), time in level 2 hypoglycemia (<54 mg/dL), time in hyperglycemia (>180 mg/dL, >250 mg/dL), hypoglycemic events (as defined in individual studies), and gastrointestinal symptoms. Patient-reported outcomes were not discussed.

A 2021 systematic review and meta-analysis by a group of Italian researchers (Dicembrini et al., 2021) included RCTs that compared effect of CGM with self-monitoring on glycemic control in pediatric and adult patients with T1D. Twenty-four studies met the inclusion criteria. The primary outcome measure was A1C, secondary endpoints included severe hypoglycemia (requiring the assistance of a third party or hospitalization) and time in range. Patient-reported secondary outcomes were health-related quality of life and treatment satisfaction. Eleven of the included studies contained quality of life measures using various assessment tools and five assessed fear of hypoglycemia.

A 2019 systematic review and meta-analysis by Japanese researchers explored CGM in patients with T2D (Ida et al., 2019). Seven RCTs with a total sample size of 669 patients met inclusion criteria. Mean age of subjects was >55 years for all included studies. All seven RCTs included A1C as an outcome measure, while three had time spent in hypoglycemia as an outcome measure. Change in body weight and blood pressure were other outcomes explored in the meta-analysis. Three studies included patient-reported outcomes: two utilized the Diabetes Treatment Satisfaction Questionnaire, and one each administered Diabetes Quality of Life, Diabetes Distress Scale, and CGM Satisfaction Scale.

A 2019 systematic review and meta-analysis by a team of Italian researchers explored the effectiveness of insulin pumps and CGM for glycemic control (Dicembrini et al., 2019) in patients with T2D. Six RCTs compared pumps with multiple daily injections, while another six compared CGM with self-monitoring. All focused on adults with T2D and none included pediatric patients. Neither total sample size nor mean age were reported. The main outcome of interest was change in A1C. Secondary outcomes of interest were severe hypoglycemia (requiring assistance of a third party or hospitalization), nocturnal rates of hypoglycemia, glucose variability, total insulin daily dose, and changes in body weight. Patient-reported secondary outcomes considered were health-related quality of life and treatment satisfaction.

Special Considerations for Patients with Disabilities, End-Stage Renal Disease, Multiple Comorbidities or Advanced Age

Of the six clinical consensus statements identified, two specifically addressed treatment of diabetes in older adults (LeRoith et al., 2019; ADA, 2023). The clinical practice guidelines for treatment of diabetes in older adults issued by the Endocrine Society and international cosponsors in 2019 (LeRoith et al., 2019) addressed glycemic control in both T1D and T2D. The authors acknowledged A1C as the gold standard to measure treatment efficacy and predict the risk of long-term complications, but they advise that A1C can have limited accuracy in the older adult population as a result of disorders such as red blood cell turnover, anemia, and chronic kidney disease, which affect A1C levels. This issue is also addressed in the ADA's discussion of glycemic control in the senior population (ADA, 2023). The recently released FDA guidance for industry (FDA, 2023) also advises that factors that affect red blood cell turnover may result in a falsely low or high A1C and adversely affect interpretation of the clinical study

effectiveness measure. As a result, the FDA advises that subjects with anemia or recent blood transfusion should be excluded in study protocols.

Endocrine Society guidelines (LeRoith et al., 2019) recommend that A1C not be used in older adults in very poor health or with very complex health conditions, defined as being in long-term care, having end-state chronic illness, having moderate-to-severe cognitive impairment, or having two or more impairments in activities of daily living. They advise that care should focus on avoiding hypoglycemia and symptomatic hyperglycemia in these cases. The ADA Standards of Care 2023 offer similar recommendations for patients ≥65 years who are in hospitals or nursing homes, have terminal illnesses or severe comorbidities, or have a diagnosis of cognitive impairment.

The ADA recommends that CGM be used for older adults with T1D and suggests it be used for those with T2D to better capture glucose variability. The Endocrine Society (LeRoith et al., 2019) recommends that treatment for patients ≥65 years be tailored specifically to minimize hypoglycemia. Because A1C does not assist in identifying hypoglycemia, the Endocrine Society recommends use of fingerstick monitoring or CGM in addition to A1C. CGM, with its ability to provide detailed assessment of glycemia in older adults, is also suggested as a means to better monitor glycemic variability.

Generalizability of the Reviewed Evidence to the Medicare Beneficiary Population

One in every three Medicare beneficiaries has diabetes and over 3.3 million Medicare beneficiaries use insulin (CMS, 2022). While T2D predominates among older Americans, a significant number of people ≥65 are living with T1D as a result of improvements in diabetes management. About 30% of patients with T2D require insulin and the likelihood of needing insulin for T2D rises with age. Older adults are often excluded from clinical trials, however, which limits input for care plans for this age group.

Of the 69 studies analyzed, 27 (39%) specifically noted the enrollment of adults ≥65, including one clinical trial and two published studies that focused solely on older adults. The majority of studies (63%) enrolling older adults focused on T1D, including all three studies that limited enrollment to older adults. Seven studies (26%) involved T2D and three (11%) enrolled individuals with both T1D and T2D. Studies enrolling older adults primarily involved CGM (44%) and CLS (41%), with only four (15%) focused on insulin pumps.

Glycemic control is fundamental to diabetes management and A1C is the primary accepted metric for glycemic control in clinical trials. Avoidance of hypoglycemia is the principal concern for older adults with T1D and insulin-using older adults with T2D (ADA 2023; LeRoith et al., 2019), because the altered mental status associated with hypoglycemia increases risk for falls, car accidents, emergency room usage, and hospitalizations. A1C provides an estimated 90-day glycemic average and cannot provide a measure of glycemic variability or hypoglycemia, leading international consensus statements—particularly those focused on older adults—to recommend that other metrics of glycemic control be included in addition to A1C. These include percent time in range (70-180 mg/dL) and various measures of hypoglycemia. A1C also has limited accuracy in older adults with anemia and chronic kidney disease, further underscoring the need for additional measures of glycemic control in studies enrolling older adults.

The sole identified consensus statement focused on older adults (LeRoith et al., 2019) recommended A1C and percent time in hypoglycemia as the preferred metrics for assessing glycemic control. The other five consensus statements recommend A1C, percent time in range, and percent time in hypoglycemia and hyperglycemia as preferred metrics. For studies enrolling older adults, time in range

(37.0%), HbA1c (33.3%), and level 1 hypoglycemia (22.2%) were the most frequent primary outcomes. Time in range was the only outcome measure which was utilized more frequently in studies that enrolled older adults (81.5%) than in studies that did not (40.0%) (p=0.0148).

Overall, while many of the studies reviewed excluded older adults or did not provide definitive information regarding age range of enrollees, the prioritized outcome measures identified included the focus on hypoglycemia that is important to the senior population. At least one measure of hypoglycemia was incorporated as an outcome measure in 96.3% of studies enrolling older adults (26/27) and in 66.7% of other studies (28/42). However, older adults may also face challenges that are not reflected in clinical trials, such as chronic health conditions, mobility and dexterity issues, and changes in cognitive function that can impact older adults' ability to use devices to manage diabetes and that impact optimal target ranges for glycemic control measures.

Consensus Assessments

There was general homogeneity in international consensus recommendations for measures of glycemic control, including A1C, time in range, and a measure of both hypoglycemia and hyperglycemia, yet very few studies actually captured all of these metrics—20% of studies overall and 30% of studies enrolling older adults. Fewer still met specific recommendations for studies involving older adults (A1C, level 1 hypoglycemia, and level 2 hypoglycemia): 6% of studies overall and 11% of studies enrolling older adults. A far larger number of studies met broad recommendations regarding the importance of hypoglycemia control for the senior population, with 43.5% of studies overall and 55.6% of studies enrolling older adults including A1C and at least one measure of hypoglycemia. As seen in **Table 7**, citation volume for prioritized outcomes ranged from a low of 49% for instances of level 1 hyperglycemia (>180 mg/dL) to a high of 71% for time in target glucose range (70-180 mg/dL).

Table 7. Consensus table

Criteria	Results of evidence synthesis
Professional consensus statements	6
Stakeholders involved	Clinical experts, researchers, professional societies, physicians, nurses, educators
Cochrane reviews in time range	0
AHRQ comparative effectiveness reviews	0
FDA Voice of the Patient reports	0
# of records used for outcomes extraction	69
# of identified outcomes (total)	21
# of prioritized outcomes	4
Citation v*olume, n range*	34-49
Citation v*olume, n median*	39
C*itation volume, % range*	49.3-71.0
Citation v*olume, % median*	56.5%

Hypoglycemia is a particular concern for older individuals with T1D and insulin-using older adults with T2D, leading international consensus statements (particularly those focused on older adults) to recommend that other metrics of glycemic control such as percent time in range (70-180 mg/dL) and various measures of hypoglycemia be included in addition to A1C. At least one measure of hypoglycemia was incorporated as an outcome measure in 96.3% of studies enrolling older adults (26/27) and in 66.7% of other studies (28/42), indicating relevance for the senior population. Nonetheless, relatively low enrollment of older adults in clinical trials and a focus on outcomes of interest to a large age range mean that many issues of relevance to older adults are not reflected in

clinical trials of devices to manage diabetes, including the limited accuracy of A1C in older adults with anemia and chronic kidney disease, and the chronic health conditions, mobility and dexterity issues, and changes in cognitive function that can impact older adults' ability to use devices to manage diabetes and that impact optimal target ranges for glycemic control measures. Further, no measures of minimal clinically important difference have been identified for any glycemic control outcomes (Hamersky et al., 2019) related to adults in general or older adults in particular, although change in A1C value of ≥0.5% is accepted as clinically significant (National Institute for Health and Care Excellence, 2015) for adults overall.

Discussion

Roughly 11.5 million of 26.8 million Americans with diabetes are ≥65 years of age, with Medicare costs that are more than double those without diabetes. While approximately 96% of older adults with diabetes have T2D (Laiteerapong et al., 2011), a significant number are living with T1D as a result of medical advances. Over 3.3 million Medicare beneficiaries with both T1D and T2D use insulin (CMS, 2022), which increases the risk of hypoglycemia, complicating management of diabetes.

Glycemic control is fundamental to management of diabetes because it reduces macro- and microvascular complications. A1C is currently the primary metric of glycemic control as it is a validated surrogate endpoint for microvascular complication risk reduction. However, since A1C cannot measure glycemic variability or hypoglycemia, professional consensus statements recommend additional metrics beyond A1C. All six consensus statements addressed limitations of A1C for measuring glucose. The sole consensus statement to focus only on older adults with diabetes (LeRoith et al., 2019) recommended A1C and percent time in level 1 (<70 mg/dL but ≥54 mg/dL) and level 2 (<54 mg/dl) hypoglycemia as outcome metrics, while recommending a focus on hypoglycemia, rather than A1C for medically complex patients. All other consensus statements recommended a combination of A1C, time in range, level 1 and level 2 hypoglycemia, and a measure of hyperglycemia (either >180 mg/dL or >250 mg/dL). However, only 20% of studies overall and 29% of studies enrolling older adults met those recommendations.

FDA

In agreement with LeRoith et al.'s guidance on older adults with diabetes (2019), the FDA has announced that it is considering a reduction in the risk of hypoglycemia to be a clinically relevant outcome measure for clinical trials alongside a reduction in or maintenance of an acceptable A1C value (FDA, 2023). Of note, the FDA does not consider time in range as an acceptable primary endpoint for glycemic control, stating that it has not been established as a surrogate for a clinical outcome.

Studies and Trials

Although sixty-nine research studies met eligibility criteria for this review and guidance, the majority were related to T1D (69.6%), compared to studies that focused on T2D (18.8%) or both types (11.6%). CGM was the device type studied most frequently (51% of studies), while 35% (24) of studies focused on CLS and 14% (10) on insulin pumps Mean enrollment was only 142 (range 25-420) with mean duration of follow-up being just 5.2 months (range 3-12 months). Enrollment of at least some older adults was confirmed for 26 published studies but only one of 21 clinical trial records—a trial that enrolled only older adults with T1D.

Prioritized Outcomes

The objective of this report was to identify the most common therapeutic outcome domains for studies of devices used to manage T1D or T2D, identify the most commonly used individual endpoints within

each domain, and compare outcomes most frequently used in clinical studies with professional recommendations. Time in range (71.0%), level 1 hypoglycemia (62.3%), HbA1c (50.7%), and level 1 hyperglycemia (49.3%) emerged as the prioritized outcome metrics, all of which fell into the physiological/clinical domain. Time in range (40.6%) and HbA1c (34.8%) were the most frequently utilized primary outcome measures.

For studies enrolling older adults, time in range (37.0%), HbA1c (33.3%), and level 1 hypoglycemia (22.2%) were the most frequent primary outcomes, while time in range (81.5%), level 1 hypoglycemia (77.8%), level 1 hyperglycemia (63.0%), HbA1c (55.6%), and level 3 hypoglycemia (55.6%) were the prioritized outcome measures overall. For unclear reasons, time in range was the only outcome measure which was utilized more frequently in studies that enrolled older adults (81.5%) than in studies that did not (40.0%) ($p=0.0148$). At least one measure of hypoglycemia was incorporated as an outcome measure in 96.3% of studies enrolling older adults and 86.7% of studies that did not enroll older adults. In the three studies limited to older adults, two used level 1 hypoglycemia as the primary outcome measure and one used time in range. A1C was not used as a primary or secondary outcome in any of the studies limited to older adults, reflecting the focus on prevention of hypoglycemia. Severe hypoglycemic events (39%) were the most frequently reported safety outcome, reported in 27 of 69 studies, followed by diabetic ketoacidosis (33%). Fifty-eight percent of studies incorporated at least one patient-reported outcome, including 48% of studies enrolling older adults.

Appendix A. Search Strategies

Set #	Strategy	Search Yield
PubMed		
January 31, 2023; Filters: in the last 3 years (1/2/2018-present), Humans, English		
9	#4 OR #6 OR #8 (2018-2023)	3,041
8	(#1 AND #7) NOT #3	2,194
7	CGM[tiab] OR "glucose meter*"[tiab] OR (glucose[tiab] AND continuous[tiab] AND (monitor*[tiab] OR sens*[tiab] OR meter*[tiab] OR device*[tiab]))	3,564
6	(#1 AND #5) NOT #3	399
5	"continuous subcutaneous insulin infusion"[tiab] OR CSII[tiab]	543
4	(#1 AND #2) NOT #3	1,421
3	comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Book Illustrations"[pt] OR congress[pt] OR annual[tiab] OR book[tiab] OR comment[tiab] OR chapter[tiab] OR note[tiab] OR review[tiab] OR symposium[tiab] OR poster[tiab] OR abstract[tiab] OR "conference paper"[tiab] OR "conference proceeding"[tiab] OR "conference review"[tiab] OR congress[tiab] OR editorial[tiab] OR erratum[tiab] OR letter[tiab] OR note[tiab] OR meeting[tiab] OR sessions[tiab] OR "short survey"[tiab] OR symposium[tiab] OR animal[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR goat[tiab] OR goats[tiab] OR pig[tiab] OR pigs[tiab] OR cadaver[tiab] OR dog[tiab] OR dogs[tiab] OR monkey[tiab] OR monkeys[tiab] OR ape[tiab] OR apes[tiab]	1,109,477
2	("insulin delivery"[tiab] AND (device*[tiab] OR system*)) OR "Insulin Infusion Systems"[Mesh] OR "insulin pump*"[tiab] OR "insulin infusion pump*"[tiab] OR "automated insulin delivery"[tiab] OR "closed loop system*"[tiab]	2,275
1	"Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR Diabet*[tiab]	145,882
Embase		
January 31, 2023		
9	(#4 OR #6 OR #8) AND [humans]/lim AND [english]/lim AND [clinical study]/lim AND [2018-2023]/py	3,021
8	#1 AND #7 NOT #3	5,915
7	cgm:ti,ab OR 'glucose meter*':ti,ab OR (glucose:ti,ab AND continuous:ti,ab AND (monitor*:ti,ab OR sens*:ti,ab OR meter*:ti,ab OR device*:ti,ab))	20,467
6	#1 AND #5 NOT #3	2,064
5	'continuous subcutaneous insulin infusion':ti,ab OR csii:ti,ab	4,978
4	#1 AND #2 NOT #3	4,980
3	'editorial'/exp OR 'letter'/exp OR 'medical illustration'/exp OR 'book'/exp OR 'poster'/exp OR 'conference abstract'/exp OR 'conference paper'/exp OR 'conferences and congresses'/exp OR	16,419,450

	'conference review'/exp OR 'erratum'/exp OR 'symposium'/exp OR 'short survey'/exp OR 'note'/exp OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR abstract:nc OR annual:nc OR conference:nc OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR meeting:nc OR sessions:nc OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR comment:ab,ti OR annual:ab,ti OR 'conference proceeding':ab,ti OR note:ab,ti OR meeting:ab,ti OR sessions:ab,ti OR 'short survey':ab,ti OR animal:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR goat:ab,ti OR goats:ab,ti OR pig:ab,ti OR pigs:ab,ti OR cadaver:ab,ti OR dog:ab,ti OR dogs:ab,ti OR monkey:ab,ti OR monkeys:ab,ti OR ape:ab,ti OR apes:ab,ti	
2	'insulin delivery':ti,ab AND (device*:ti,ab OR system*) OR 'insulin pump'/de OR 'insulin pump*':ti,ab OR 'insulin infusion pump*':ti,ab OR 'automated insulin delivery':ti,ab OR 'closed loop system*':ti,ab	16,332
1	'non insulin dependent diabetes mellitus'/de OR 'insulin dependent diabetes mellitus'/de OR diabet*:ti,ab	1,206,172
Clinicaltrials.gov		
February 2, 2023		
#1	Searched (“diabetes” or “diabetes mellitus”) AND (”monitor*”), interventional studies, start date on or after 01/01/2018	280
#2	Searched (“diabetes” or “diabetes mellitus”) AND “pump”, interventional studies, start date on or after 01/01/2018	205

Appendix B. Summary of Prioritized Outcomes Investigated in Primary Studies

The following two tables present the key outcomes identified for all adults (Table B1) and for older adults only (Table B2) in the primary studies reviewed for this report. The first five clinical or qualitative (patient-reported) primary outcomes, the first five clinical secondary outcomes, and the first five qualitative (patient-reported) secondary outcomes listed were extracted from each study record. The clinical outcomes were then prioritized and only the prioritized outcomes are reported here. Patient-reported outcomes were not prioritized. All patient-reported outcomes related to quality of life. All safety and resource outcomes were also extracted and were not prioritized.

Table B1. Summary of efficacy outcomes prioritized in each outcome domain, all studies involving adults (n=69)

Outcome Domain and Outcomes	Citation Volume	Primary/Secondary Outcome Citation Volume	Common endpoints
PHYSIOLOGICAL/CLINICAL (only the prioritized outcomes appear here)			
time in range	49	28 (40.6%) / 21 (30.4%)	• percent of time in target glucose range (70-180 mg/dL) • percent time per day/night in target range • percent time in tight target glucose range (70-140 mg/dL) • noninferiority or superiority of time in range
Level 1 hypoglycemia (<70 mg/dL)	43	11 (15.9%) / 32 (46.4%)	• percent time with glucose <70 mg/dL • number of events with sensor glucose <70 mg/dL • number of events with ≥15 consecutive minutes with sensor glucose <70 mg/dL • percent time in nocturnal hypoglycemia • percent time in daytime hypoglycemia
A1C	35	24 (34.8%) / 11 (15.9%)	• mean absolute or relative change in A1C • superiority/non-inferiority of A1C difference • variation in A1C • proportion attaining target A1C value (<7%, <7.5%, etc.)
Level 1 hyperglycemia (>180 mg/dL)	34	1 (1.4%) / 33 (47.8%)	• percentage of time spent with glucose >180 mg/dL • number of events with sensor glucose >180 mg/dL • number of events with ≥15 consecutive minutes with senor glucose >180 mg/dL • duration of hyperglycemic events
RESOURCE UTILIZATION			

healthcare utilization	4	0 / 4 (5.8%)	• healthcare utilization per count of inpatient/outpatient visits • emergency department visits • hospitalizations • cost per patient of healthcare for emergency room visits • hyperglycemia resulting in treatment at a healthcare facility
ADVERSE EVENTS			
serious adverse events	13	0 / 13 (18.8%)	number of serious adverse events
adverse events	9	0 / 9 (13.0%)	number of adverse events
LIFE IMPACT			
quality of life	40	2 (2.9%) / 38 (55.1%)	• pre/post differences in quality of life measures • differences between intervention and control group in quality of life measures

Table B2. Summary of efficacy outcomes prioritized in each outcome domain, studies that enrolled older adults (n=27)

Outcome Domain and Outcomes	Citation Volume	Primary/Secondary Outcome Citation Volume	Common endpoints
PHYSIOLOGICAL/CLINICAL			
time in range	22	10 (37.0%) / 12 (44.4%)	• percent of time in target glucose range (70-180 mg/dL) • percent time per day/night in target range • percent time in tight target glucose range (70-140 mg/dL) • noninferiority or superiority of time in range
Level 1 hypoglycemia (<70 mg/dL)	21	6 (22.2%) / 15 (55.6%)	• percent time with glucose <70 mg/dL • number of events with sensor glucose <70 mg/dL • number of events with ≥15 consecutive minutes with sensor glucose <70 mg/dL • percent time in nocturnal hypoglycemia • percent time in daytime hypoglycemia
Level 1 hyperglycemia (>180 mg/dL)	17	0 /17 (63.0%)	• percentage of time spent with glucose >180 mg/dL • number of events with sensor glucose >180 mg/dL • number of events with ≥15 consecutive minutes with senor glucose >180 mg/dL • duration of hyperglycemic events
Level 3 hypoglycemia (requires assistance)	15	1 (3.7%) / 14 (51.8%)	• number of severe hypoglycemic events

			• number of patients with severe hypoglycemia
A1C	15	9 (33.3%) / 6 (22.2%)	• mean absolute or relative change in A1C • superiority/non-inferiority of A1C difference • variation in A1C • proportion attaining target A1C value (<7%, <7.5%, etc.)
RESOURCE UTILIZATION			
healthcare utilization	1	0 / 1 (3.7%)	hyperglycemia resulting in treatment at a healthcare facility
ADVERSE EVENTS			
serious adverse events	13	0 / 13 (48.2%)	number of serious adverse events
adverse events	9	0 / 9 33.3%)	number of adverse events
LIFE IMPACT			
quality of life	13	0 / 13 (48.2%)	• pre/post differences in quality of life measures • differences between intervention and control group in quality of life measures

Table B3. Details of prioritized instruments, quality of life outcomes (n=69)

Instrument	Citation volume (%), all studies of adults (n=69)	Citation volume (%), studies that enrolled older adults (n=27)	MCID	Instrument properties (e.g., items, dimensions, recall, description, etc.)	Validity/reliability
Diabetes Distress Scale	12 (17.4%)	3 (11.1%)	In a 2016 study by Fisher et al., MCID for adult patients with T1D was identified as +/−0.19 but varied by subscale (.26 to .50). The same team established cut points for high distress among patients with T2D: little or no distress, <2.0; moderate distress, 2.0–2.9; high distress, ≥3.0 (Fisher et al., 2012)	The 17-item DDS assesses diabetes distress in adults with T1D or T2D. Each item is rated on a 6-point scale from 1 (not a problem) to 6 (a very significant problem). the scale yields an overall distress score based on the average of responses for all 17 items and scores for each of four subscales (emotional burden, physician distress, regimen distress, interpersonal distress). A total or subscale score >2.0 (moderate distress) is considered clinically significant.	Originally developed for and validated in a U.S. population (Polonsky et al., 2005), with reliability and validity measured across four diverse sites: waiting room at a primary care clinic (n=200), waiting room at a diabetes specialty clinic (n=179), a diabetes management study program (n=167), and an ongoing diabetes management program (n=158). Subsequently validated in a number of other languages, including Mandarin (Zhang et al., 2022), Spanish (Martinez-Vega et al., 2016), Malay (Chew et al., 2015), and Bengali (Akter et al., 2022).
Diabetes Treatment Satisfaction Questionnaire	11 (15.9%)	4 (14.8%)	not established	The DTSQ contains eight items scored on a 7-point scale (from -3 to +3). Six items measure Treatment Satisfaction (satisfaction with current treatment, convenience,	The DTSQ is a proprietary instrument first developed in the early 1980s. It is widely used, particularly in clinical trials, but also for routine

				flexibility, intention to continue with current treatment, etc.) and two questions measure perceived frequency of hyper- and hypoglycemia. Items summed to produce a total Treatment Satisfaction score, with a minimum value of -18 and a maximum value of +18; a higher score indicates greater treatment satisfaction. In case of missing items, overall score calculated as the mean of the available items. Low scores on the two items measuring perception of hyper- and hypoglycemia represent good perceived blood glucose control.	clinical monitoring, and is available in more than 100 languages. It has been validated with data from clinical trials, specialty clinics, and diabetes management programs. (Bradley et al., 1994; Bradley et al., 2009)
Hypoglycemia Fear Survey	9 (13.0%)	4 (14.8%)	Stargardt et al. (2009) established MCID for the Worry Scale of the Hypoglycemia Fear Survey using a combination of distribution-based and anchor-based methods, but their work was based on non-insulin dependent individuals with T2D. In their RCT comparing device-administered and self-administered	The 33-item HFS-II is comprised of a 15-item Behavior (behaviors to avoid hypoglycemia) and 18-item Worry (specific concerns about hypoglycemia) subscale. Responses are made on 5-point Likert scale where 0=never and 4=almost always. Scores are obtained by summing the items for the subscales and adding scales together for total score. Higher scores indicate higher fear of hypoglycemia and greater avoidance behaviors.	The original Hypoglycemia Fear Survey (HFS) (Cox 1987) was developed in US in 1987 to assess the levels of fear related to hypoglycemia in adults with T1D. The tool was initially developed with input from healthcare providers and diabetic patients and was validated with insulin-requiring diabetic patients. The latest revision of the survey, HFS-II, has been shown to be a valid and reliable measure of fear of

			insulin in patients with T2D, Davies et al. (2019) defined MCID as half of the standard deviation of the HFS score at baseline, although justification for that decision was not provided.		hypoglycemia (Gonder-Frederick et al., 2011) which has also been used in studies of patients with T2D (Huang et al., 2022; Hajos et al., 2014).
Problem Areas in Diabetes	6 (8.7%)	not a prioritized instrument for studies enrolling older adults	de Wit et al. (2022) identified cutoffs for clinically meaningful distress in the 20-item PAID: ≥ 40 to detect people with high levels of diabetes-distress; a score of 0–16 indicates low diabetes distress and a score of 17–39 moderate diabetes distress. MCID for the PAID-5 is not established.	The PAID-5 questionnaire consists of 5 questions with answers ranging from 0 (not a problem) to 4 (serious problem). Total score calculated as the sum of the individual questions, resulting in a number between 0 and 20, where lower scores represent lower distress.	Designed by William Polonsky, the original PAID was a 20-item measure of emotional adjustment to life with diabetes. Validity was initially established in a study of 451 insulin-requiring women with T1D or T2D (Polonsky et al., 1995). Validity was subsequently confirmed in a study of 256 volunteer diabetic outpatients (Welch e al., 1997). A shortened version, the PAID-5, was developed and validated for rapid screening of diabetes-related emotional distress (McGuire 2010).

Appendix C. Citations for Included Publications

48 Publications Included in Data Analysis
Abraham MB, de Bock M, Smith GJ, et al. Effect of a Hybrid Closed-Loop System on Glycemic and Psychosocial Outcomes in Children and Adolescents With Type 1 Diabetes: A Randomized Clinical Trial. JAMA Pediatr. 2021;175(12):1227-35.
Abraham MB, Nicholas JA, Smith GJ, et al. Reduction in Hypoglycemia With the Predictive Low-Glucose Management System: A Long-term Randomized Controlled Trial in Adolescents With Type 1 Diabetes. Diabetes Care. 2018;41(2):303-10.
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Al Hayek AA, Robert AA, Al Dawish MA. Effectiveness of the Freestyle Libre Flash Glucose Monitoring System on Diabetes Distress Among Individuals with Type 1 Diabetes: A Prospective Study. Diabetes Therapy. 2020;11(4):927-37.
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Aronson R, Abitbol A, Tweden KS. First assessment of the performance of an implantable continuous glucose monitoring system through 180 days in a primarily adolescent population with type 1 diabetes. Diabetes Obes Metab. 2019;21(7):1689-94.
Aronson R, Brown RE, Chu L, et al. IMpact of flash glucose Monitoring in pEople with type 2 Diabetes Inadequately controlled with non-insulin Antihyperglycaemic ThErapy (IMMEDIATE): A randomized controlled trial. Diabetes, Obesity and Metabolism. 2022.
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Benhamou PY, Franc S, Reznik Y, et al. Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. Lancet Digit Health. 2019;1(1):e17-e25.
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Appendix D. Citations for Eligible clinicaltrials.gov Records

Table D1. Eligible clinicaltrials.gov records (n=21)

NCT Number	Title	Status	Device	Start Date	Completion Date	US/OUS*
NCT03445065	A French Study to Evaluate the Usefulness of an Implantable Continuous Glucose Monitoring (CGM) Sensor to Improve Glycemic Control in Participants With Diabetes Mellitus	Completed	CGM	28-Feb-18	20-Aug-20	OUS
NCT03478969	Participant-Reported Outcomes With the Accu-Chek Solo Micropump System	Completed	pump	17-May-18	18-May-20	OUS
NCT03620357	Continuous Glucose Monitoring & Management In Type 2 Diabetes (T2D)	Completed	CGM	5-Sep-18	4-Nov-20	OUS
NCT03908125	Post Approval Study of the Eversense Continuous Glucose Monitoring	Active, not recruiting	CGM	19-Mar-19	Mar-23	US
NCT03959423	Safety Evaluation of the Advanced Hybrid Closed Loop (AHCL) System	Active, not recruiting	pump	24-Jul-19	22-Dec-22	US
NCT04016662	Automated Insulin Delivery in Elderly With Type 1 Diabetes (AIDE T1D)	Recruiting	pump	28-Sep-20	31-Dec-23	US
NCT04223973	MEDTRUM A7+ TouchCare Insulin Patch Pump (MedInPS)	Completed	pump	29-Jan-20	1-Jun-21	OUS
NCT04266379	Efficacy of Closed-loop Insulin Therapy in Adults Prone to Hypoglycemia	Recruiting	CLS	13-May-20	3-Feb-23	OUS
NCT04413578	CGM - Reimagine Primary Care	Completed	CGM	1-Dec-18	31-Dec-19	US
NCT04436796	The International Diabetes Closed Loop (iDCL) Trial: Protocol 4	Completed	CLS	5-Aug-20	10-May-21	US
NCT04721158	CGM Use in Children With Type 2 Diabetes	Completed	CGM	17-Jan-21	28-Jul-22	US
NCT04902378	Closed-loop Insulin Delivery In Type 1 Diabetes Pregnancies (CIRCUIT)	Recruiting	CLS	15-Jun-21	Jan-26	OUS

NCT05131139	Enhance Study: Evaluation of Accuracy and Safety of the Eversense CGM System With Enhanced Features	Recruiting	CGM	20-Oct-21	30-Jan-24	US
NCT05238142	In-Home Study With MiniMed 780G Pump Automated Control in Type 2-Evaluation of the AHCL System in Adults With Insulin-requiring Type 2 Diabetes	Recruiting	pump	25-Feb-22	May-23	US
NCT05325294	Evaluation of the Advanced Hybrid Closed Loop (AHCL) System in Type 1 Adults and Pediatrics Utilizing Lyumjev	Recruiting	CLS	5-May-22	1-Jul-23	US
NCT05360056	Continuous Glucose Monitoring Following Hospital Discharge	Recruiting	CGM	26-Apr-22	Mar-24	US
NCT05403502	Safety Evaluation of an Advanced Hybrid Closed Loop System Using Lyumjev With the Tandem t:Slim X2 Insulin Pump With Control-IQ Technology in Adults, Adolescents and Children With Type 1 Diabetes	Recruiting	CLS	31-Aug-22	22-May-23	
NCT05409131	Omnipod 5 System Compared to Pump Therapy	Recruiting	pump	7-Jul-22	Jun-23	OUS
NCT05477030	Effect of Automated Insulin Delivery on Early-stage Diabetic Complications	Recruiting	pump	23-Feb-22	23-Feb-24	OUS
NCT05523362	Feasibility and Clinical Utility of the Dexcom G6 Continuous Glucose Monitoring Device for Type 2 Diabetes	Recruiting	CGM	15-Dec-22	1-Oct-23	US
NCT05669547	Dual Hormone Closed Loop in Type 1 Diabetes	Not yet recruiting	CLS	Jan-23	1-Apr-24	

*Studies with location in and outside the US are classified as OUS

Abbreviations: CGM=continuous glucose monitor, CLS=closed loop system, OUS=outside the US

Appendix E. Citations for Included Consensus Statements

Professional organization	Citation
Advanced Technologies & Treatments for Diabetes (ATTD) Congress (recommendations endorsed by the American Diabetes Association, American Association of Clinical Endocrinologists, American Association of Diabetes Educators, European Association for the Study of Diabetes, Foundation of European Nurses in Diabetes, International Society for Pediatric and Adolescent Diabetes, JDRF, and Pediatric Endocrine Society)	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;42:1593-1603.
American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange	Agiostratidou G, Anhalt H, Ball D, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40:1622-1630.
American Association of Clinical Endocrinologists, the American Diabetes Association, the Association of Diabetes Care and Education Specialists, DiabetesIndia, the European Association for the Study of Diabetes, the International Society for Pediatric and Adolescent Diabetes, the Japanese Diabetes Society, and the Juvenile Diabetes Research Foundation	Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinology. 2023;11:42-57.
American Association of Clinical Endocrinology	Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. Endocrine Practice. 2021;27:505-537.
American Diabetes Association	American Diabetes Association. (2018). Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care*, *41*(5), 917-928. https://doi.org/10.2337/dci18-0007
Endocrine Society, European Society of Endocrinology, Gerontological Society of America, and Obesity Society	LeRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of diabetes in older adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2019;104:1520–74.

Appendix F. Citations for Included Systematic Reviews

Dicembrini I, Cosentino C, Monami M, et al. Effects of real-time continuous glucose monitoring in type 1 diabetes: a meta-analysis of randomized controlled trials. Acta Diabetol. 2021;58(4):401-10.
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Ida S, Kaneko R, Murata K. Utility of Real-Time and Retrospective Continuous Glucose Monitoring in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. J Diabetes Res. 2019;2019:4684815.
Zeng B, Jia H, Gao L, et al. Dual-hormone artificial pancreas for glucose control in type 1 diabetes: A meta-analysis. Diabetes Obes Metab. 2022;24(10):1967-75.

Appendix G. Overview of Screening Process

Figure G1. Screening of publications

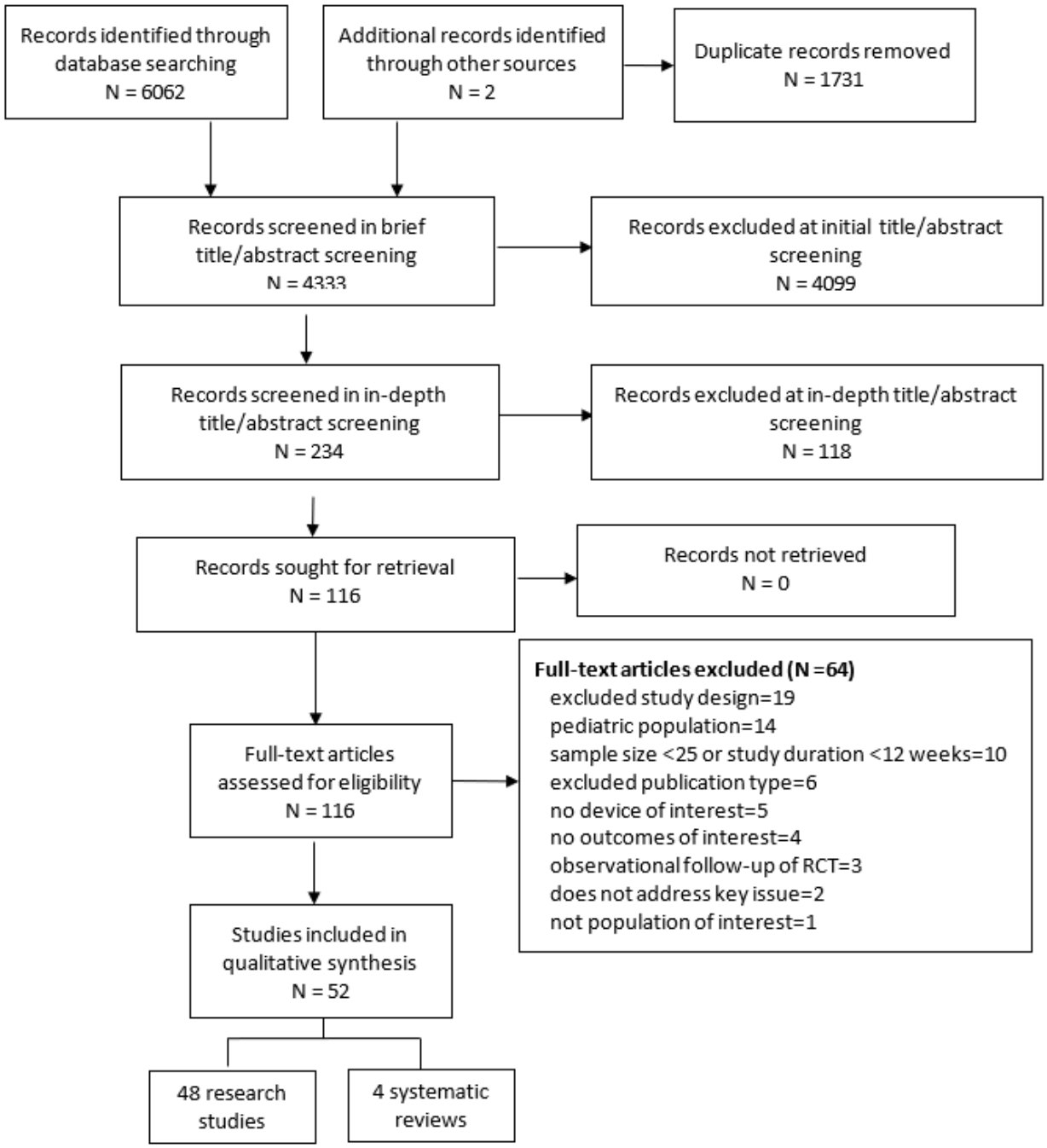
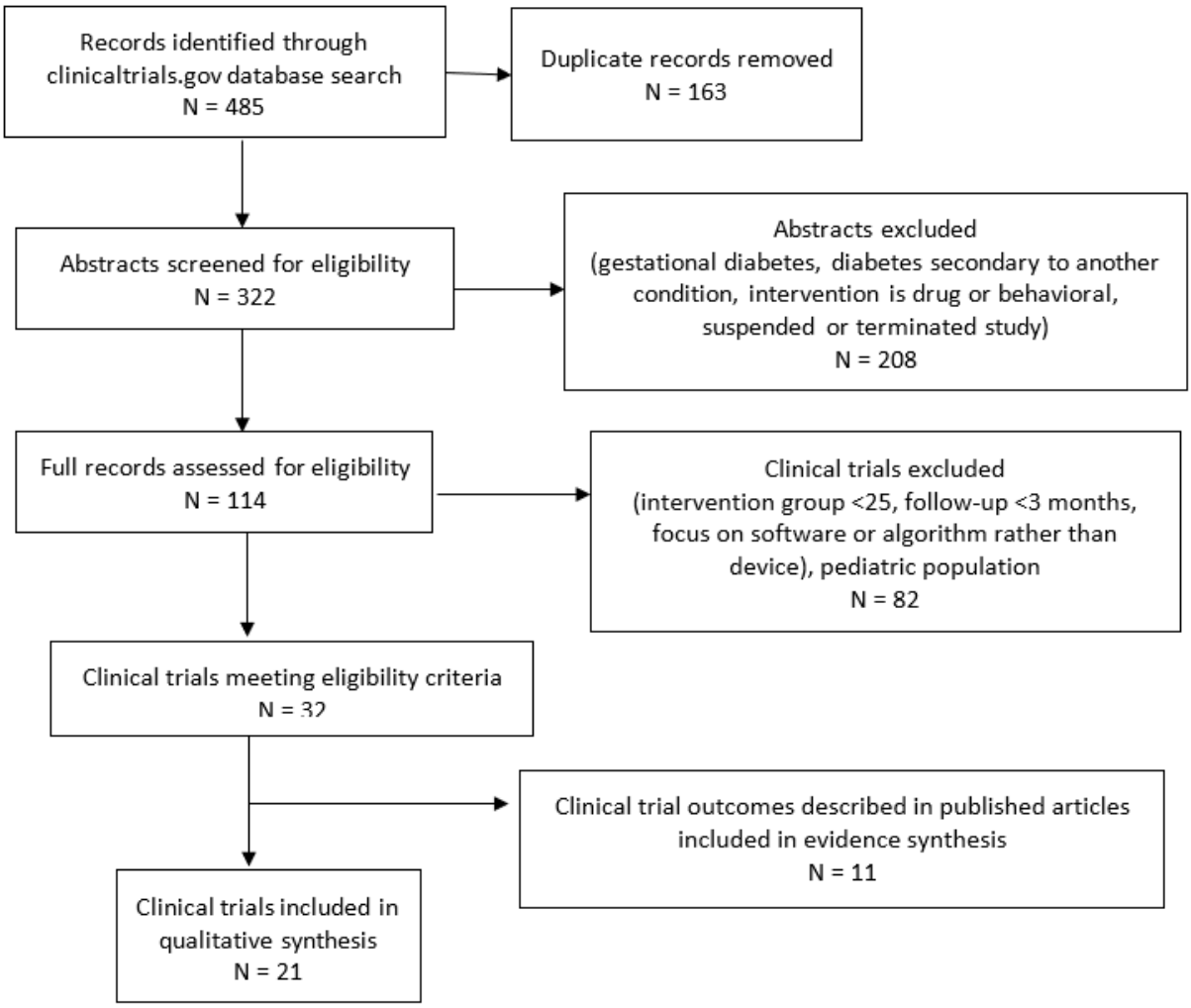


Figure G2. Screening of clinicaltrials.gov records



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