Clinical Endpoints Review, Executive Summary

Devices for Self-management of Type 1 and Insulin-Dependent Type 2 Diabetes

Contents

Summary of the Clinical Endpoints Review (CER)

The CER for this topic investigated three types of literature: statements arising from formal consensus processes (e.g., Delphi panels), clinical studies of self-management devices for patients with diabetes (both published and listed on Clinicaltrials.gov), and systematic reviews of such clinical studies. Table A1 in this document lists, by domain, the most important clinical endpoints according to those three sources. Only one of the six consensus statements issued guidance specific to older adults. Only 27 of 69 clinical studies enrolled older adults. None of these 27 studies reported results separately for older study participants, but the clinical endpoints used in these 27 studies are listed separately. The four identified systematic reviews presented no analysis specific to older adults.

Clinical endpoints belonging to the Surrogate Markers domain were prioritized according to citation volume; only the most frequently cited of these endpoints appear in Table A1. Table A2 lists all the surrogate markers investigated in primary studies and considered for prioritization.

The CER identified few definitions of minimal clinically important differences (MCIDs) across the three sources. MCIDs were identified for some of the quality of life instruments. A published systematic review failed to find any definitions of MCIDs for glucose control endpoints. However, the CER identified an MCID for change in A1c. Table B lists the targets identified for acceptable percentages of time spent by the patient within, below, and above an acceptable range of glucose control values.

According to the CER, A1c is considered by the FDA to be a validated surrogate endpoint for microvascular risk reduction. Validation of the other surrogate markers is not addressed in the CER, but the CER reports validation for all of the diabetes-specific quality of life instruments in Appendix Table B3.

Table A1. Clinical Endpoints Identified in the Literature (see following page for definitions and footnotes)

CLINICAL ENDPOINTS IDENTIFIED		MCID DEFINITIONS
For all adults	**For older adults (age ≥65 yrs)**	
6 professional consensus statements (Table 2 in CER)*		
• A1c (6 statements) • Hypoglycemia (<70 mg/dL) (6 statements) • Level 2 hypoglycemia (<54 mg/dL) (6 statements) • Time in range (5 statements) • Level 2 hyperglycemia (>250 mg/dL) (5 statements) • Level 1 hyperglycemia (>180 mg/dL) (4 statements) • Time in diabetic ketoacidosis (1 statement) • Coefficient of variation (1 statement)	1 statement†: • A1C • Hypoglycemia (<70 mg/dL) • Level 2 hypoglycemia (<54 mg/dL) A1C should be used for glucose monitoring only on the basis of shared decision making for patients with high disease complexity (poor health), defined as: long-term care, end-state chronic illness, moderate to severe cognitive impairment, or ≥2 impairments in ADL.	None identified
Endpoints cited in primary studies; 69 studies, 27 of which enrolled older adults (Appendices B1, B2 and B3 in CER)‡		
Prioritized Surrogate Markers (listed in decreasing order of frequency)¶		
• Time in range • Level 1 hypoglycemia (<70 mg/dL) • A1C • Level 1 hyperglycemia (>180 mg/dL)	• Time in range • Level 1 hypoglycemia (<70 mg/dL) • Level 1 hyperglycemia (>180 mg/dL) • Level 3 hypoglycemia (requires assistance, i.e., severe event characterized by altered mental and/or physical status requiring assistance from another person) • A1C	None identified in a systematic review of glycemic outcomes NICE and ADA: change in A1c of >0.5% is accepted as clinically significant
Patient-Reported Outcomes ("Life Impact Domain" in the CER)		
QOL was the only patient-reported ("qualitative" in the CER) endpoint that met selection criteria. Investigated in 40 of 69 studies, 38 times as an exploratory endpoint.	QOL was the only patient-reported endpoint that met selection criteria. Investigated in 13 of 27 studies, always as an exploratory endpoint	All 4 instruments identified in the CER have been validated; MCIDs have been identified for 3.
Safety ("Adverse Events" Domain in the CER)		
• Serious adverse events (13 of 69 studies)§ • Any adverse event (9 of 69 studies)	• Serious adverse events (13 of 27 studies) • Any adverse event (9 of 27 studies)	None identified
Other Observations		
• No studies evaluated more than 3 of the 5 endpoints most commonly recommended by professional associations, and few studies evaluated as many as 3 (Table 5 and text in CER). • Differences in volume of citation (p. 15 of the CER) o Level 2 hypoglycemia (<54 mg/dL) more common in T1D than in T2D (39.6% vs 7.7%, p=0.04) o Time in range more common for CLS than for pump or CGM (92% vs 70% vs 57%; p=0.0113) o CLS studies were more likely than pump or CGM studies to use level 2 (p=0.02) or level 3 (p=0.01) hypoglycemia as endpoints o Mean glucose (p=0.01) and diabetic ketoacidosis (p=0.01) more likely in CLS studies than for pump or CGM o **Time in range was the only endpoint to differ in frequency between studies that enrolled older adults (more frequent) than in studies that did not (less frequent) (p=0.01).**		
4 systematic reviews (all meta-analyses) *(Table 6 in CER)*		
• 3 reviews addressed A1C, time in range, and severe hypoglycemia • 1 review addressed A1C and time in range • 2 addressed PROs		

Definitions and Footnotes for Table A1

ADA, American Diabetes Association; ADL, activities of daily living; CER, Clinical Endpoints Review; CLS, closed loop systems; CGM, continuous glucose monitoring; NICE, The National Institute for Health and Care Excellence; QOL, quality of life; T1(2)D, type 1(2) diabetes

*Issued by Advanced Technologies & Treatments for Diabetes Congress (2019), American Association of Clinical Endocrinology (2023), American Association of Clinical Endocrinology (2021), American Association of Clinical Endocrinology (2017), American Diabetes Association (2023), Endocrine Society (2019).

†Issued by Endocrine Society (2019). American Diabetes Association (2023) also advocated not using A1c in patients in very poor health.

‡These endpoints were abstracted from each study: the first 5 primary endpoints, the first 5 clinical secondary endpoints, the first 5 secondary qualitative endpoints, and any resource use or safety endpoints. From those lists, clinical endpoints were prioritized if they accounted for at least 50% of the cumulative number of endpoint citations across studies. All qualitative, resource use, and safety endpoints from those lists are presented here.

¶See Table A2 for the complete selection of surrogate endpoints, which were labeled "physiological/clinical endpoints" in the CER.

§Details regarding specific adverse events were not provided in the CER.

Table A2. All Surrogate Markers Investigated in Primary Studies

Prioritized endpoints (which thus appear in Table A1) are highlighted in yellow. These endpoints were referred to as "physiological/clinical" outcomes in the CER.

Endpoint	For all adults (total n, 69 studies)	For older adults (total n, 27 studies)*
time in range	**49**	**22**
level 1 hypoglycemia (<70 mg/dL)	**35**	**21**
level 1 hyperglycemia (>180 mg/dL)	**34**	**17**
A1c	**34**	**15**
level 3 hypoglycemia (requires assistance of another person)	30	**15**
diabetic ketoacidosis	25	11
mean glucose	18	8
level 2 hyperglycemia (>250 mg/dL)	11	5
level 2 hypoglycemia (<54 mg/dL)	22	10
mean absolute relative difference of device and venous readings (MARD)	5	2
level 3 hyperglycemia (>300 mg/dL)	5	**4**
monitoring frequency	3	0
sensor longevity	2	1
Clarke Error Grid	2	0
glucose variability	2	0
days of CGM use	1	0
current diabetes standards	1	0
diabetic angiopathy markers	1	0

*Issued by Endocrine Society (2019). American Diabetes Association (2023) also advocated not using A1c in patients in very poor health.

NOTE: The Clarke Error Grid evaluates the clinical significance of inaccuracies in blood glucose concentration measurements.

Table B. Surrogate Marker Targets for Percent Time at Different Glucose Levels

Data reviewed in CER	All adults		Older adults	
Goals according to 3 professional consensus statements* ***(Table 3 in CER)***	A1c	<7% or individualized	A1c	<7.0-<7.0-<7.5% in healthy older adults, <8% with intermediate disease complexity.† Do not use in patients with high disease complexity (poor health) (focus on hypoglycemia)‡
	Time in [target glucose] range	>70%	Time in range	>50%
	Level 1 hypoglycemia (<70 mg/dL)	<4%	Level 1 hypoglycemia (<70 mg/dL)	<1%
	Level 2 hypoglycemia (<54 mg/dL)	<1%	Level 2 hypoglycemia (>54 mg/dL)	~0% (a difficult target to meet without assistance of a device)
	Level 1 hyperglycemia (>180 mg/dL)	<25%	Level 1 hyperglycemia (>180 mg/dL)	<10%
	Level 2 hyperglycemia (>250 mg/dL)	<5%	Level 2 hyperglycemia (>250 mg/dL)	<10%
ADA, UK NICE ***(text in CER)***	A1C value of >0.5% is accepted as clinically significant			

ADA, American Diabetes Association; NICE, National Institute for Health and Clinical Excellence

*Issued by Advanced Technologies & Treatments for Diabetes Congress (2019), American Association of Clinical Endocrinology (2023), American Association of Clinical Endocrinology (2021)

†Intermediate disease complexity is defined as ≥3 nondiabetes chronic illnesses and/or 1 of the following: ≥2 impairments in activities of daily living (ADLs) or mild cognitive impairment.

‡High disease complexity (poor health) is defined as: long-term care, end-state chronic illness, moderate to severe cognitive impairment, or ≥2 impairments in ADL.