Guidelines on insulin use for type 1 diabetes in adults, including in emergency and humanitarian settings



World Health Organization

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Cover photo: A person living with type 1 diabetes administers an insulin injection at home in Kumi, Uganda - © WHO / Badru Katumba

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Abbreviations and acronyms

BMI	body mass index
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CGM	continuous glucose monitoring
CI	confidence interval
CUA	cost-utility analysis
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DOI	declaration of interests
EDIC	Epidemiology of Diabetes Interventions and Complications
ERG	External Review Group
EtD	evidence-to-decision
GAD	glutamic acid decarboxylase
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HbA1c	glycated haemoglobin A1c
IA-2A	islet antigen-2 antibodies
IAA	insulin autoantibodies
ICA	islet cell antibodies
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
isCGM	intermittently scanned continuous glucose monitoring
IU	international unit
LMICs	low- and middle-income countries
MCID	minimal clinically important difference
MD	mean difference
NCD	noncommunicable disease
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
PEN	WHO package of essential noncommunicable (PEN) disease interventions for primary health care
PHC	primary health care
PICO	population, intervention, comparator and outcome
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
rtCGM	real-time continuous glucose monitoring
SMBG	self-monitoring of blood glucose
WHO	World Health Organization
WTP	willingness-to-pay
ZnT8A	zinc transporter 8 autoantibody

Glossary

Continuous glucose monitoring (CGM)	Frequent automated measurement of interstitial glucose concentrations using a subcutaneous sensor, including real-time CGM (rtCGM) or intermittently scanned CGM (isCGM).
Cost-effectiveness analysis (CEA)	An economic evaluation of the costs and health outcomes of two or more interventions, expressing results as a cost per unit of health benefit gained.
Deterministic sensitivity analysis	A method used in health economic modelling to assess the influence of uncertainty by varying individual input parameters one at a time across chosen plausible ranges while holding all other parameters constant. Also referred to as one-way sensitivity analysis.
Diabetic ketoacidosis (DKA)	A life-threatening condition in an individual with diabetes characterized by fluid and electrolyte depletion, high blood glucose levels and metabolic acidosis.
Dominant	Describes an intervention with consequences that are both more effective and costs less than one or more specified comparators.
Glycated haemoglobin A1c (HbA1c)	Haemoglobin glycated by non-enzymatic binding of glucose to haemoglobin. It is the most widely used measure of glycaemic control in both clinical trials and diabetes management, reflecting mean blood glucose level over the previous 8–12 weeks.
Human insulin	Insulin identical in amino acid sequence to endogenous human insulin, produced by recombinant DNA technology. Includes regular human insulin (short-acting) and neutral protamine Hagedorn (NPH) insulin (intermediate-acting).
Hypoglycaemia	Potentially life-threatening low concentration of blood glucose, most frequently a side-effect of pharmacological treatment. There is no universally agreed definition. In studies the definitions of hypoglycaemia are most frequently in the range <2.8 to 4.0 mmol/L. Severe hypoglycaemia is most frequently defined as a symptomatic condition that requires the assistance of a third person for correcting blood glucose levels.
Incremental cost-effectiveness ratio (ICER)	The difference in cost between two interventions divided by the difference in their effectiveness, representing the additional cost per additional unit of health benefit with the more costly intervention.
Insulin analogues	Insulins different from those occurring in nature and derived from human insulin by modifying its structure to change the pharmacokinetic profile.

Insulin analogues (long-and ultra long-acting)	Insulin analogues used as basal insulin for the management of diabetes mellitus, administered by subcutaneous injection and provide prolonged basal insulin replacement. Examples: • glargine • detemir • degludec • icodec
Insulin analogue (rapid-and ultra rapid-acting)	Insulin analogues used as bolus insulin for the management of diabetes mellitus, administered by subcutaneous injection and provide mealtime insulin replacement. Examples: • lispro • aspart • glulisine • faster-acting aspart
Intermittently scanned CGM (isCGM)	A CGM system in which the user actively scans a subcutaneous sensor with a separate device to obtain a current glucose reading and short trend history. Unlike rtCGM, isCGM does not generate automatic alerts by default.
Neutral Protamine Hagedorn (NPH or isophane) insulin	An intermediate-acting insulin used in type 1 and type 2 diabetes. It is produced by crystallizing zinc-insulin-protamines at neutral pH. It is called neutral protamine Hagedorn for inventor Hans Christian Hagedorn.
Real-time CGM (rtCGM)	A CGM system that continuously displays current glucose concentration and trend direction and generates automatic alerts for hypoglycaemia and hyperglycaemia without requiring user action to obtain blood glucose values.
Self-monitoring of blood glucose (SMBG)	Measurement of capillary blood glucose by the patient using a portable glucometer and a finger-prick blood sample, or isCGM or rtCGM providing point-in-time glucose readings to guide insulin dose adjustments and detect hypoglycaemia.
Type 1 diabetes	Diabetes caused by the destruction of pancreatic beta-cells, most commonly by an immune-mediated process, resulting in lack of insulin production by the pancreas and need for insulin injections for survival.
Urine glucose testing	Detection of glucose in urine using dipstick tests as an indirect method of glycaemic monitoring and detection of ketosis.
Willingness-to-pay (WTP) threshold	The maximum cost per unit of health benefit that a decision-maker or health system is prepared to pay; an intervention with an ICER below this threshold is considered cost-effective.

Executive summary

Introduction

Type 1 diabetes mellitus is a chronic autoimmune condition characterized by absolute insulin deficiency and a lifelong requirement for insulin therapy to maintain survival. Approximately 9.5 million people had type 1 diabetes globally in 2025, with more than 500 000 new cases diagnosed. Although the condition has historically been associated with childhood and adolescent onset, a substantial proportion of new cases occur in adults, and the adult population with type 1 diabetes continues to grow. Prevalence and incidence vary substantially across regions, with the highest reported incidence in Northern Europe, and lower but increasing incidence in many countries classified by the World Bank as being low- and middle-income countries (LMICs).

Inequities in survival and health outcomes exist across settings and populations. In high-income settings, improvements in insulin availability, monitoring technologies and structured clinical care have contributed to increased life expectancy. In many LMICs, survival remains closely linked to health system capacity, with limited access to insulin and blood glucose monitoring, shortages of trained health-care workers and high out-of-pocket costs continuing to result in preventable morbidity and premature mortality. The management of type 1 diabetes is further complicated in emergency and humanitarian settings, where interrupted supply chains, unreliable cold-chain infrastructure and limited health-care worker experience in insulin management increase the risk of adverse outcomes.

Diabetes is the only major noncommunicable disease for which premature mortality has continued to increase in recent decades. In response, the World Health Organization (WHO) launched the Global Diabetes Compact in 2021, and Member States subsequently endorsed global diabetes coverage targets, including the commitment that 100% of people with type 1 diabetes should have access to affordable insulin treatment and blood glucose self-monitoring by 2030. Substantial gaps between committing to and implementing policy persist, particularly in LMICs. Existing clinical guidance has largely been developed in high-income settings, and may not always be feasible or appropriate to implement in low-resource or humanitarian environments.

Type 1 diabetes differs from type 2 diabetes in its underlying pathophysiology and clinical management with different use of insulin. People with type 1 diabetes require lifelong insulin therapy because of absolute insulin deficiency. In contrast, type 2 diabetes is characterized by insulin resistance and relative insulin deficiency. Type 1 diabetes is often under-recognized and misclassified as type 2 diabetes, particularly where incidence is low or access to diagnostic tools and specialist care is limited. Delayed or missed diagnosis results in delayed prescription of insulin or treatment with an inappropriate insulin regimen and contributes to high rates of diabetic ketoacidosis at presentation and is associated with increased mortality. Adults with type 1 diabetes frequently experience fragmented care, limited access to specialist support and inconsistent follow-up, increasing the risk of acute metabolic complications and long-term complications.

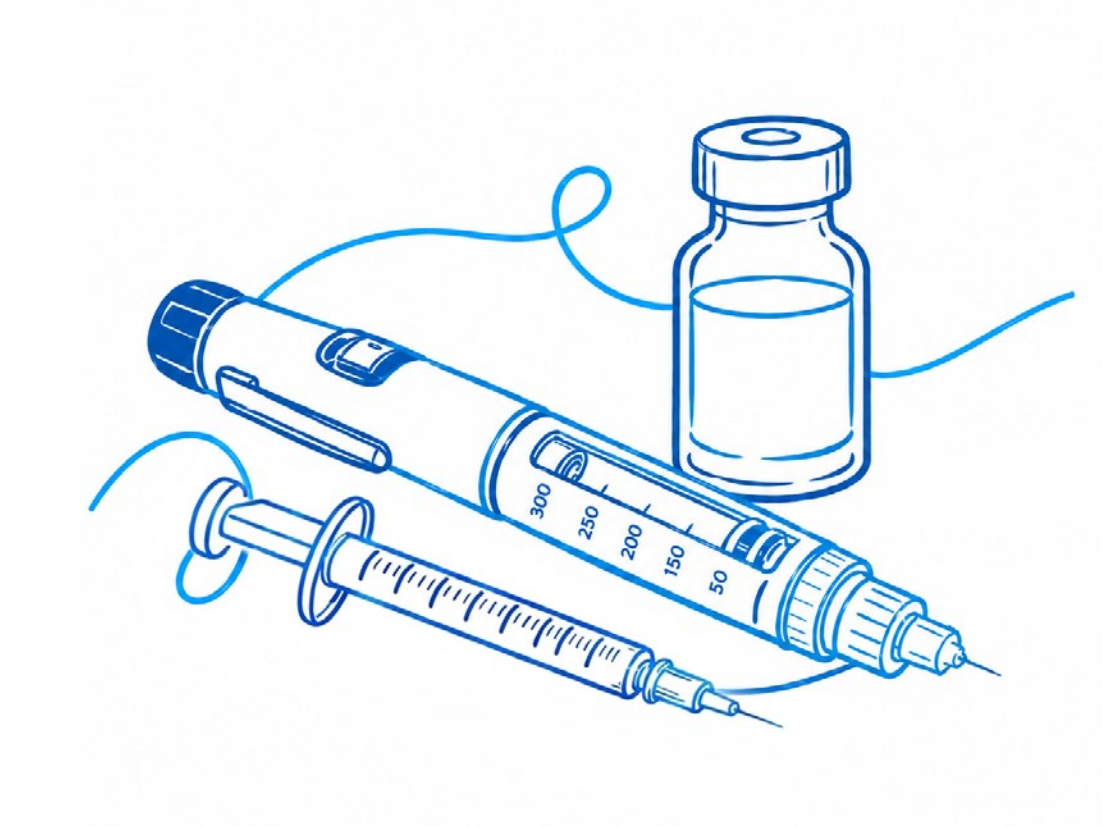
WHO has previously published *Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus (2018) and the WHO package of essential noncommunicable (PEN) disease interventions for primary health care (2020).* However, these publications did not cover other aspects of insulin use for adults with type 1 diabetes. This guideline updates and expands WHO recommendations on insulin use for adults with type 1 diabetes by providing recommendations on specificities in diagnosis and classification, insulin regimens, insulin types and modes of insulin delivery, clinical monitoring of glycaemic control and self-monitoring of glycaemia.

Purpose, scope and target audience

The purpose of this guideline is to provide evidence-based recommendations on insulin use to manage type 1 diabetes in adults, applicable across a range of health system settings and contexts, including low-resource, emergency and humanitarian settings. The guideline is intended to support safe, effective and feasible insulin use while promoting equity and continuity of care.

The scope of the guideline includes:

- diagnosis and classification considerations relevant to type 1 diabetes in adults;
- insulin regimens, insulin types and modes of insulin delivery;
- clinical monitoring of glycaemic control; and
- self-monitoring of glycaemia.



The guideline does not address insulin use in people under 18 years of age, during pregnancy; clinical management of acute complications of diabetes and established long-term diabetes-related complications; or, finally, interventions requiring advanced technologies or specialist services not widely available in LMICs or humanitarian settings, such as insulin pumps, automated insulin delivery systems or intravenous insulin regimens.

The guideline applies to adults aged 18 years and older with type 1 diabetes, including those with newly diagnosed disease, those receiving treatment, those with suspected type 1 diabetes but who have previously been classified with another type of diabetes and adults diagnosed below the age of 18 years who have transitioned to adult care.

The primary audience is health-care providers involved in the management of adults with type 1 diabetes across a range of settings, including primary, secondary and tertiary care and emergency and humanitarian contexts. The guideline is also intended to support policy-makers, national programme managers, procurement and supply-chain officers, health workforce training institutions and international organizations and humanitarian agencies involved in diabetes care.

Guideline development methods

The guideline was developed in accordance with the process described in the *WHO handbook for guideline development* and under the oversight of the WHO Guidelines Review Committee (GRC). The development process was coordinated by the WHO Department of Noncommunicable Diseases and Mental Health, with methodological support from an independent guideline methodologist and governance oversight by an internal WHO Steering Group.

WHO convened an external Guideline Development Group (GDG) comprising 19 members with multidisciplinary expertise in clinical care, public health, diabetes epidemiology, health systems, humanitarian health and including individuals with type 1 diabetes. Members were selected to ensure balanced representation across WHO regions, gender and professional backgrounds. Three independent evidence synthesis teams, commissioned through a competitive process, conducted a total of 13 systematic reviews to inform the priority questions. Priority questions were developed using the population, intervention, comparison and outcome (PICO) framework and addressed diagnosis and classification, insulin regimens and delivery, clinical monitoring of glycaemic control and self-monitoring of glycaemia.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to appraise the certainty of the evidence for benefits and harms of each prioritized intervention. The GDG applied the GRADE evidence-to-decision (EtD) framework, based on the Developing and Evaluating Communication Strategies to support Informed Decisions and Practice based on Evidence framework, to structure discussions and formulate recommendations. EtD domains included the balance of benefits and harms, certainty of evidence, values and preferences, resource implications, equity, acceptability and feasibility. The GDG met four times and formulated recommendations through structured discussions and consensus. An External Review Group provided independent technical review of the draft guideline prior to finalization.

Recommendations

The guideline contains recommendations across four clinical domains: diagnosis and classification; insulin therapy (covering insulin regimens, bolus insulins, basal insulins, insulin mixing and insulin delivery); clinical monitoring of glycaemic control; and self-monitoring of glycaemia. One recommendation is strong; the remaining 13 are conditional. The sole strong recommendation reflects the GDG's high level of confidence that the benefits of this regimen outweigh the harms for most adults in most circumstances. Conditional recommendations indicate that the expected benefits outweigh harms for most people, but that individual circumstances, resource constraints or values and preferences may appropriately influence clinical decisions; shared decision-making is therefore encouraged for these recommendations.

All recommendations apply to adults with type 1 diabetes across a range of health system settings. Particular attention is given throughout to feasibility in low-resource, emergency and humanitarian contexts, where supply continuity, health-care workforce capacity and access to monitoring technologies may be constrained. Each recommendation is accompanied by remarks that clarify application in practice, address contextual factors and identify subgroups or circumstances requiring additional consideration.



Table 1. Summary of recommendations

Category	No	Recommendation
Diagnosis and classification	**1**	Consider diabetes-specific biomarkers, such as pancreatic islet cell autoantibodies and serum/plasma C-peptide, when a diagnosis of type 1 diabetes in adults is uncertain. *(conditional recommendation, very low certainty)*
Insulin use	**2a**	Use intensified insulin therapy (multiple daily injections with dose adjustment to blood glucose values) for adults with type 1 diabetes. *(strong recommendation, moderate certainty)*
	2b	Consider intensified insulin therapy for adults with type 1 diabetes in emergency and humanitarian settings. *(conditional recommendation, low certainty)*
	3a	Either human insulin or insulin analogues can be used as bolus insulin. Human insulin is the preferred option because it is in general less costly. *(conditional recommendation, moderate certainty)*
	3b	Consider ultra rapid-acting insulin analogues as bolus insulin at mealtimes or after meals for adults with type 1 diabetes. *(conditional recommendation, very low certainty)*
	4a	Either human insulin or insulin analogues can be used as basal insulin. Human insulin is the preferred option because it is in general less costly. *(conditional recommendation, moderate certainty)*
	4b	Consider once-daily long-acting insulin analogues at the time of day preferred by the adult with type 1 diabetes. *(conditional recommendation, low certainty)*
	5	Consider premixed human insulin or self-mixed human insulin (NPH and regular human insulin drawn from separate vials or injected from separate pens) for adults with type 1 diabetes. *(conditional recommendation, very low certainty)*
Insulin delivery	**6**	Consider pens over syringes to deliver insulin in adults with type 1 diabetes. *(conditional recommendation, very low certainty)*
Clinical monitoring of glycaemic control	**7**	Offer HbA1c testing at up to three-monthly intervals to adults with type 1 diabetes. *(conditional recommendation, low certainty)*
	8	Aim to achieve an HbA1c of ≤ 7.0% (53 mmol/mol) in most adults with type 1 diabetes. *(conditional recommendation, moderate certainty)*

Category	No	Recommendation
Self-monitoring of glycaemia	**9**	Consider self-monitoring by fingerstick testing, real-time continuous glucose monitoring (rtCGM) or intermittently scanned (flash) continuous glucose monitoring (isCGM) in adults with type 1 diabetes. *(conditional recommendation, moderate certainty)*
	10	Consider frequent self-monitoring of blood glucose in adults with type 1 diabetes, three or more times per day. *(conditional recommendation, very low certainty)*
	11	Consider urine glucose testing in adults with type 1 diabetes when blood glucose testing is not available for self-monitoring. *(conditional recommendation, low certainty)*

Implementation considerations

WHO intends people to implement the recommendations in this guideline as a coherent set of options that support adults with type 1 diabetes to receive appropriate insulin therapy, monitoring and clinical follow-up. Given the chronicity and complexity of type 1 diabetes management, health-care providers should select, tailor and sequence interventions according to the clinical needs, preferences and circumstances of the individual, guided by the principles of person-centred care, availability, accessibility, acceptability, quality and safety, comprehensive care and balance between best established care and feasibility at scale.

For recommendations involving selecting a type of insulin, either human insulin or insulin analogues can be used as bolus or basal insulin. Human insulin (regular human insulin as bolus and NPH insulin as basal) is the preferred option because it is generally less costly. Insulin analogues may be considered in specific clinical circumstances, such as persistent severe or nocturnal hypoglycaemia despite appropriate use of human insulin and optimization of diabetes education. Decisions to use insulin analogues should weigh availability, affordability, sustainability of supply and equity implications.

Strengthening blood glucose monitoring, diabetes education and health-care worker training are identified as essential enabling conditions for the safe and effective use of intensified insulin therapy and other recommended interventions. In settings where preferred interventions are not feasible due to supply constraints or health system limitations, contingency planning and context-adapted approaches are explicitly addressed in the remarks accompanying relevant recommendations.

Successfully implementing this guideline will require countries to align with their national policies for diabetes care, essential medicines lists and programmes to develop the health workforce. WHO will support implementation through country-level technical assistance, adaptation tools and monitoring frameworks. Countries should designate mechanisms to account for updating and monitoring implementation and ensure that people with type 1 diabetes participate in designing and evaluating the programme.

1 Introduction



1.1 Global context and rationale for developing WHO guidance

Type 1 diabetes mellitus is a chronic condition characterized by absolute insulin deficiency and a lifelong requirement for insulin to maintain survival *(1)*. Type 1 diabetes differs from type 2 diabetes in its underlying pathophysiology and consequent different use of insulin in clinical management because type 2 diabetes is characterized by insulin resistance and relative, rather than absolute, insulin deficiency *(2).* Type 1 diabetes is associated with a high risk of avoidable morbidity and premature mortality in the absence of timely diagnosis, access to insulin and appropriate clinical care and glucose self-monitoring *(3).* Worldwide, approximately 9.5 million people had type 1 diabetes in 2025, with more than 500 000 new cases every year *(1, 4, 5).* Prevalence, incidence and mortality vary substantially across regions, and although type 1 diabetes has historically been considered a disease of childhood and adolescence, evidence shows that a substantial proportion of new cases occur in adulthood *(4, 6).* In some settings, type 1 diabetes is under-recognized and misclassified as type 2 diabetes, particularly where the incidence is low or access to diagnostic tools or specialist care is limited *(5, 7).* Delayed or missed diagnosis contributes to high rates of diabetic ketoacidosis (DKA) at presentation and is associated with increased mortality *(8).*

Although most people with type 1 diabetes live in high-income countries, the condition causes disproportionately worse outcomes in low-resource settings because of inequities in care. In high-income countries, improvements in insulin availability, structured specialized clinical follow-up and access to multidisciplinary care have led to increased life expectancy *(4, 5).* In contrast, in many LMICs, survival remains closely linked to health system capacity *(4).* Limited availability and affordability of insulin, inadequate access to blood glucose monitoring and shortages of trained health-care workers continue to result in preventable disability and mortality *(9).*

Management of type 1 diabetes requires continuous clinical care, including appropriate insulin therapy, regular monitoring of glycaemic status and education to support self-management *(10).* For adults, these requirements are frequently affected by transitions between paediatric and adult services, competing

social and economic responsibilities, and, in some settings, high out-of-pocket expenditures *(11).* Evidence from diverse settings indicates that adults with type 1 diabetes often experience fragmented care, limited access to specialist support and inconsistent follow-up, increasing the risk of acute metabolic complications, long-term diabetes-related complications and reduced health-related quality of life (5, 7).

People with type 1 diabetes are at particular risk in emergency and humanitarian settings, where health systems may be disrupted by conflict, displacement, natural disasters or economic instability *(12).* In such contexts, insulin supply chains are vulnerable to interruption, cold-chain infrastructure may be unreliable and health-care workers may have limited experience in insulin initiation and dose adjustment *(13).* Clinical guidance developed primarily for well-resourced health systems may not always be feasible or appropriate in these environments, underscoring the need for context-appropriate recommendations that support continuity of care.

Beyond acute risks, type 1 diabetes is associated with significant long-term morbidity and socioeconomic impact *(14).* Suboptimal glycaemic control increases the risk of microvascular and macrovascular complications, including kidney disease, visual impairment, neuropathy, cardiovascular disease and premature death *(15).* These complications impose substantial costs on individuals, families and health systems, contributing to reduced productivity and widening health inequities *(16).*

Diabetes is prioritized within the Sustainable Development Goals and is the only major noncommunicable disease (NCD) for which premature mortality has continued to increase in recent decades *(17).* In response, the World Health Organization launched the Global Diabetes Compact in 2021 to reduce diabetes risk and ensure access to equitable, comprehensive, affordable and quality treatment and care *(18).* Member States subsequently endorsed global diabetes coverage targets, including the commitment that 100% of people with type 1 diabetes should have access to affordable insulin treatment and blood glucose self-monitoring by 2030 *(19).*

Despite these commitments, substantial gaps remain between policy objectives and implementation, particularly in LMICs, where challenges related to procurement, pricing, regulation and distribution persist. Changes in global insulin markets, along with limitations in health-care workforce capacity and access to monitoring tools, may further constrain the safe and effective use of insulin *(20).*

Existing clinical guidance on insulin use for type 1 diabetes has largely been developed in high-income settings and often assumes stable supply chains, advanced monitoring technologies and specialist-led care. Guidance specific to adults with type 1 diabetes, including those diagnosed later in life, has received comparatively limited attention, despite the growing adult population with the condition.

This guideline addresses some of these gaps by providing WHO recommendations on insulin use for adults with type 1 diabetes, applicable across a range of health system contexts. Specifically, the guideline provides recommendations on diagnosis, insulin regimens and delivery, clinical monitoring of glycated haemoglobin A1c (HbA1c) and self-monitoring of glycaemia, with attention to feasibility, equity and continuity of care, including in emergency and humanitarian settings.

1.2 Scope of the guideline

This guideline provides evidence-based recommendations on the use of insulin for the management of type 1 diabetes mellitus in adults.

The scope of the guideline includes:

- diagnosis and classification considerations relevant to type 1 diabetes in adults;
- insulin regimens, insulin types and modes of insulin delivery;
- clinical monitoring of glycaemic control; and
- self-monitoring of glycaemia.

The recommendations are informed by priority questions developed using the PICO framework and are based on systematic reviews of the best available evidence. Decision-making considers benefits and harms, certainty of the evidence, feasibility, equity, acceptability and resource implications.

The guideline does not address:

- clinical management of acute complications of diabetes and established long-term diabetes-related complications;
- interventions that require advanced technologies, infrastructure or specialist services, including insulin pumps and automated insulin delivery, insulin use in DKA, insulin in combination with metformin or glucagon-like peptide-1 (GLP-1) receptor agonists, intravenous insulin regimens, inpatient dose-adjustment devices and insulin use during surgery; and
- broader aspects of patient education not directly related to safe insulin use and monitoring.

1.3 Target populations and settings

This guideline applies to adults (aged ≥18 years) with type 1 diabetes[1].

The target population includes:

- adults with newly diagnosed type 1 diabetes, including those presenting for the first time and suspected of having type 1 diabetes on clinical grounds;
- adults with established type 1 diabetes receiving ongoing insulin treatment;
- adults in whom type 1 diabetes is suspected but have been previously classified as another type of diabetes, where diagnostic confirmation may influence management; and
- adults diagnosed in childhood or adolescence who have transitioned to adult care.

The guideline does not apply to:

- people younger than 18 years with type 1 diabetes;
- people with diabetes during pregnancy; and
- people with other forms of diabetes, except where diagnostic reclassification as type 1 diabetes is under consideration.

[1] WHO defines adults as individuals aged ≥20 years and adolescents as those aged 10–19 years. The population addressed by this guideline was defined according to the eligibility criteria of the underlying evidence, which may include participants classified as older adolescents under WHO age definitions. Medicines regulatory bodies do not require insulin trials to distinguish between ages 18–19 years and 20 and above.

1.4 Intended audience

This guideline is intended primarily for health-care providers involved in managing adults with type 1 diabetes across a range of health system contexts, including routine care and emergency or humanitarian settings. The recommendations focus on clinical decision-making and are designed to support safe, effective and feasible insulin use.

The guideline will be of particular relevance to:

- medical doctors, nurses, pharmacists and other trained health-care workers providing care for adults with type 1 diabetes in primary, secondary or tertiary care settings;
- non-specialist health-care providers involved in insulin initiation, adjustment and follow-up, especially in primary care and community-based services;
- health-care providers working in emergency and humanitarian settings, including conflict-affected areas, displacement settings and disrupted health services; and
- people with type 1 diabetes and their caregivers, as well as community and patient organizations, to support informed engagement in care.

In addition, the guideline is intended to support:

- policy-makers and national or subnational programme managers responsible for developing, adapting or updating diabetes care policies, clinical protocols and essential medicines lists;
- procurement and supply-chain officers involved in decisions related to insulin types, delivery devices and glucose-monitoring technologies;
- institutions responsible for pre-service and in-service training of health-care workers, to inform clinical education and capacity-building; and
- international organizations, humanitarian agencies and nongovernmental organizations supporting diabetes care in low-, middle- and high-income settings.

1.5 Relationship to existing WHO guidance

This guideline is aligned with the World Health Assembly resolution WHA74.4 on strengthening the prevention and control of diabetes and the global diabetes coverage targets, in particular target 5: that 100% of people with type 1 diabetes should have access to affordable insulin treatment and blood glucose self-monitoring by 2030 *(19)*. The guideline supports the implementation of these global commitments by providing evidence-based recommendations on the use of insulin for adults with type 1 diabetes, with explicit consideration of feasibility, equity and continuity of care, including in emergency and humanitarian settings.

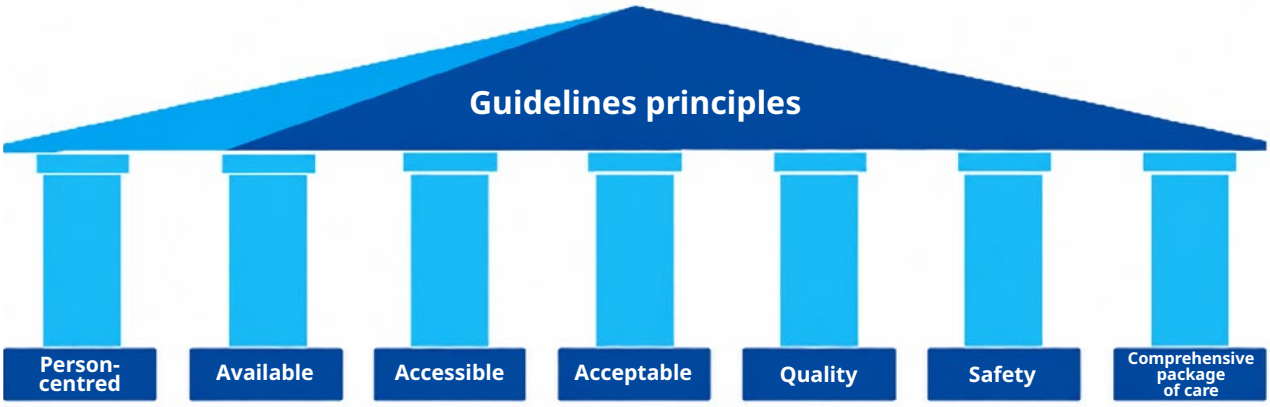
This guideline updates and expands previous WHO normative guidance relevant to insulin therapy in adults with diabetes. In particular, it builds on the *Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus (21).* It addresses priority clinical questions relevant to insulin use in adults with type 1 diabetes that are not fully covered in earlier WHO guidelines.

The guideline is consistent with the *WHO package of essential noncommunicable (PEN) disease interventions for primary health care,* which outlines insulin as an essential component of diabetes care at first-level health facilities *(22).* It provides more detailed, evidence-based recommendations to support safe and effective insulin use within primary care systems and across different levels of health system capacity.

This guideline is distinct from *WHO consolidated guidelines for the management of common childhood illness: management of type 1 diabetes mellitus in children and adolescents* and from *WHO recommendations on care for women with diabetes during pregnancy,* which address specific populations outside the scope of the present recommendations.

The guideline also aligns with *WHO guidance on global monitoring for diabetes prevention and control (23),* by supporting standardized approaches to diagnosis, monitoring of glycaemic control and tracking of access to essential diabetes medicines and health technologies.

1.6 Guiding principles



- Widest possible access at the population level
- Balance between the best-established standard of care and what is feasible on a large scale

Fig. 1. Guiding principles.

The recommendations in this guideline are underpinned by the following principles (Fig. 1):

1. Person-centred care

Care for adults with type 1 diabetes should recognize the lifelong dependence on insulin, accommodate the need for self-management and consider clinical risk, life circumstances and patient preferences.

2. Availability

Insulin therapy and essential monitoring required to safely manage type 1 diabetes should be available across levels of the health system, and adapted to the country context and referral pathways. The guidelines' recommendations prioritize insulin regimens, delivery methods and monitoring approaches that can be sustained within existing supply chains and health system capacity.

3. Accessibility

Guidance emphasizes the widest possible access at the population level. Recommendations are framed to reduce barriers related to cost, geography, workforce constraints and health system disruption, including in low-resource, emergency and humanitarian settings.

4. Acceptability

Insulin regimens and monitoring approaches should be acceptable to both people with type 1 diabetes and health-care providers. Consideration is given to treatment burden, feasibility of self-monitoring, risk of hypoglycaemia and the capacity of non-specialist providers to deliver care safely.

5. Quality

High-quality clinical care depends on accurate diagnosis and classification, appropriate insulin therapy, regular clinical monitoring and self-monitoring of glycaemia, and prevention of avoidable acute complications.

6. Safety

Safe care for adults with type 1 diabetes requires continuity of care, measures to minimize preventable treatment-related harm and support for safe self-management.

7. Comprehensive package of care

Effective insulin use requires integrating it within a broader package of diabetes care, including diagnosis, clinical monitoring and self-monitoring of glycaemia. The guideline addresses these interrelated components to support consistent and coherent care across settings.

The guideline seeks to promote the widest possible access to effective insulin therapy and monitoring at the population level, while balancing the best established standards of care with what is feasible to implement at scale across diverse settings. Where evidence supports multiple options, recommendations allow flexibility for country adaptation according to available resources, health system capacity and local context.



2 Methods



2.1 Guideline development process

This guideline was developed in accordance with the procedures and standards set out in the *WHO handbook for guideline development* and under the oversight of the WHO Guidelines Review Committee (GRC) *(24).* The process followed WHO requirements for transparency, methodological rigour and management of conflicts of interest. WHO convened an independent GDG comprising clinical experts, methodologists, public health specialists and community representatives with experience across different health system contexts. An independent guideline methodologist supported the GDG throughout the process.

The GDG formulated priority questions using the PICO framework and selected questions that addressed key aspects of insulin use for adults with type 1 diabetes relevant to clinical decision-making across a range of settings, including primary care, referral facilities and emergency or humanitarian contexts where continuity of insulin therapy may be disrupted. The GDG gave particular attention to questions raised during scoping regarding diagnostic uncertainty, selecting insulin types and regimens and monitoring glucose. The GDG also considered the feasibility of implementing the guidance in resource-constrained or unstable settings where preferred interventions might not be feasible and alternative approaches might be necessary to preserve life and lower the risk of complications. The GDG agreed on priority outcomes for decision-making.

Systematic reviews were commissioned for each priority question, and evidence was synthesized using methods appropriate to the available data (sections 2.5 and 2.6). A total of 13 systematic reviews were conducted to inform the recommendations in this guideline. The certainty of the evidence was assessed using the GRADE approach *(25).* Where applicable, network meta-analyses and economic evaluations were considered alongside direct comparisons. GRADE Evidence Profile summaries were prepared for each PICO question and shared with the GDG in advance of recommendation formulation.

During the GDG meetings, the EtD approach was used to structure discussions and support consistent decision-making across several domains (section 2.7). The framework was based on the Developing and Evaluating Communication Strategies to support Informed Decisions and Practice based on Evidence framework *(26).*

Recommendations were formulated following structured discussion (section 2.7). The direction (in favour or against an intervention) and strength (strong or conditional) of each recommendation reflected the overall balance of effects, certainty of evidence and contextual considerations across EtD domains. Variability in judgements was documented in the corresponding EtD tables. Detailed EtD judgement summaries are presented in the annexes.

All GDG members, external reviewers and other relevant external contributors completed WHO declarations of interests in accordance with WHO policy.

2.2 Contributors and roles

2.2.1 WHO Steering Group

The Steering Group comprised WHO staff members from headquarters and regional offices, bringing together expertise in noncommunicable diseases, emergency and humanitarian health, innovation and health technologies and health economics. Members were drawn from the WHO Department of Noncommunicable Diseases and Mental Health; the WHO Department of Innovation and Emerging Technologies; the WHO Department of Health Financing and Economics; the WHO Health Emergencies Programme; the Pan American Health Organization (PAHO); the WHO Regional Office for Europe; and the WHO Regional Office for the Eastern Mediterranean.

The Steering Group provided overall administrative, procedural and technical oversight throughout the guideline development process. Its responsibilities included defining the scope and objectives of the guideline; drafting and refining the priority questions in PICO format; preparing and submitting the guideline proposal for review by the WHO GRC; overseeing the selection and appointment of the GDG, the independent guideline methodologist and the evidence synthesis teams; organizing and supporting GDG meetings; supervising the evidence synthesis process; and reviewing the final guideline document prior to submission to the WHO GRC and for publication. Members of the WHO Steering Group are listed in Annex 1.

2.2.2 Guideline Development Group (GDG)

The GDG comprised 19 members with multidisciplinary expertise relevant to the management of type 1 diabetes in adults. Members were selected by WHO to ensure balanced representation across WHO regions, gender and professional backgrounds, and to reflect a range of health system contexts, including LMICs and emergency or humanitarian settings. The GDG included clinicians, public health experts, academics, representatives from humanitarian organizations and individuals with type 1 diabetes, with expertise spanning across endocrinology, primary care, diabetes epidemiology, health systems and humanitarian health.

The GDG met four times. The first meeting, held virtually in March 2024, focused on finalizing the scope of the guideline, priority PICO questions and critical and important outcomes for decision-making. The second meeting, held in-person on 1–4 December 2025, examined and interpreted the findings of the systematic reviews and applied the EtD framework to formulate draft recommendations. The third and fourth meetings, held virtually on 4 and 12 March 2026, focused on discussion of remaining

priority questions, final consideration of evidence for outstanding PICOs, ensuring consistency across recommendations and reaching consensus on the final set of recommendations. Members of the GDG and records of attendance are listed in Annex 2.

2.2.3 Guideline methodologist

WHO appointed an independent guideline methodologist to support the guideline development process and to ensure methodological rigour and adherence to WHO standards for guideline development. The methodologist advised on the formulation and refinement of priority questions, guided the GDG in the appraisal and interpretation of evidence and facilitated the application of the EtD framework during GDG meetings. The methodologist supported transparent, structured and consensus-based GDG discussions and provided methodological input to promote consistency in judgements across recommendations.

2.2.4 Evidence synthesis teams

WHO commissioned independent evidence synthesis teams to conduct systematic reviews to inform the development of this guideline. All evidence syntheses were conducted in accordance with WHO standards for guideline development and applied the GRADE methodology.

Following an open and competitive call for expressions of interest, three evidence synthesis teams were selected based on demonstrated technical expertise, experience in conducting systematic reviews for WHO and other international organizations and capacity to deliver high-quality evidence syntheses within agreed timelines. The teams were: the Knowledge Synthesis and Application Unit, University of Ottawa (Canada); PROPUL Evidence LLP (India); and the Medical Faculty of Heinrich Heine University Düsseldorf (Germany).

Each team was responsible for conducting one or more systematic reviews addressing priority questions within the scope of the guideline, including diagnosis and classification, insulin regimens and delivery, clinical monitoring of glycaemic control and self-monitoring of glycaemia. The teams developed prespecified review protocols, conducted literature searches, assessed risk of bias, synthesized quantitative evidence and other relevant evidence inputs as appropriate, and prepared GRADE evidence profiles and EtD tables. Members of the evidence synthesis teams presented their findings to the GDG and responded to technical questions but did not participate in the formulation of recommendations.

2.2.5 External Review Group

An External Review Group (ERG) provided independent review of the draft guideline prior to finalization. The ERG comprised technical experts with relevant clinical, public health and health systems expertise in diabetes care, insulin use and guideline implementation, selected to complement the expertise of the GDG and to ensure balanced geographic and disciplinary representation. Declarations of interests were reviewed, and no conflicts were identified that were judged to preclude participation.
The role of the ERG was to review the draft guideline for technical accuracy, clarity, coherence and consistency with WHO standards and policies. ERG members provided comments on the interpretation of evidence, the clarity and applicability of recommendations and considerations for implementation.

The ERG did not participate in formulating or modifying the recommendations, which remained the responsibility of the GDG. However, its feedback was considered by the WHO Steering Group in finalizing the guideline document, and any major disagreements were documented.

2.3 Declarations of interests

All members of the GDG, the ERG, the guideline methodologist and other external contributors were required to complete a WHO declaration of interests (DOI) form prior to participation in the guideline development process, in accordance with WHO policy. They were also required to inform WHO of any changes in their interests during the guideline development process. Before each GDG meeting, members were given an opportunity to update or amend their declarations.

Declarations of interests were reviewed by the WHO Steering Group using the criteria set out in the *WHO handbook for guideline development.* The review considered the nature, value, relevance and timing of each declared interest, whether it was financial, academic or intellectual and whether it was personal or non-personal. These factors informed the assessment of potential conflicts of interest and any necessary management measures.

Most GDG members declared no relevant interests and were permitted to participate fully. One GDG member was excluded from decision-making on recommendations related to the area pertaining to the declared interest. A summary of the declarations of interests and how they were managed is provided in Annex 3.

2.4 Priority questions and outcomes (PICOs)

The WHO Steering Group developed an initial set of draft questions based on the scope and objectives of the guideline, existing WHO recommendations and key gaps in guidance related to insulin use for adults with type 1 diabetes. The GDG reviewed, refined and finalized the PICO questions during its first meeting, considering clinical relevance, public health importance, applicability across different health system contexts and feasibility of implementation, including in low-resource and humanitarian settings.

For each PICO question within the scope (see Section 1.2), the GDG identified and scored outcomes for decision-making using the GRADE approach, selecting outcomes classified as critical or important for formulating recommendations. These prioritized outcomes guided the scope of the systematic reviews and subsequent EtD discussions.

2.5 Evidence identification and synthesis

Evidence to inform this guideline was identified through systematic reviews commissioned by WHO for each priority question. Reviews were conducted according to prespecified protocols agreed with WHO and the independent guideline methodologist and aligned with the PICO questions prioritized by the GDG. Systematic searches were undertaken in major bibliographic databases and trial registries, including MEDLINE (via PubMed), Embase and the Cochrane Central Register of Controlled Trials (CENTRAL), supplemented by searches of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, reference list screening and targeted searches for ongoing or unpublished studies.

Eligibility criteria were specified a priori for each review. Comparative effectiveness questions (e.g. insulin regimens, insulin types and delivery devices) prioritized randomized controlled trial (RCT), while diagnostic accuracy and classification questions (biomarkers) included eligible diagnostic study designs as defined in the review protocols. Study selection, data extraction and risk of bias assessment were undertaken using duplicate processes, with disagreements resolved by discussion.

Evidence on effectiveness

For each priority question, evidence on effectiveness and harms was synthesized using methods appropriate to the available data. Risk of bias was assessed using validated tools matched to study design (e.g. Cochrane risk-of-bias tools for randomized trials and design-appropriate tools for diagnostic accuracy studies).

Where studies were sufficiently homogeneous, pairwise meta-analyses were conducted. For questions involving multiple competing interventions with a connected evidence network, notably comparisons of insulin types, network meta-analyses were undertaken to estimate relative effects using both direct and indirect evidence. These analyses included assessment of network coherence and sensitivity analyses to explore the robustness of findings. Where quantitative pooling was not appropriate, results were summarized narratively.

The certainty of evidence for critical and important outcomes was assessed using the GRADE approach. Evidence profiles and summary of findings tables were prepared and provided to the GDG in advance of recommendation formulation. Evidence synthesis teams presented their findings during GDG meetings and responded to technical questions, but did not participate in decision-making or formulation of recommendations.

Evidence on values and preferences, acceptability and feasibility

No additional primary studies or formal qualitative evidence syntheses were commissioned specifically for this guideline to address values and preferences, acceptability or feasibility. Judgements in these domains were informed by consideration of information reported in some of the included effectiveness studies (such as preferences, treatment burden, adherence, device discontinuation, training requirements and follow-up intensity), as well as by the multidisciplinary expertise of the GDG, including members with lived experience of type 1 diabetes and experience across diverse health system contexts. These considerations were explicitly addressed during GDG discussions and documented within the EtD framework.

Evidence on resource use and cost-effectiveness

Evidence on resource use and cost-effectiveness was informed through complementary evidence inputs addressing costs, affordability and economic considerations related to insulin therapies, delivery devices and monitoring approaches. This included reviews of available economic evaluations as well as targeted analyses of insulin prices and monitoring-related costs commissioned by WHO.

Economic evidence identification followed systematic approaches consistent with WHO standards, with structured extraction of key characteristics including perspective, cost components, time horizon and relevance across settings. For self-monitoring modalities, evidence addressed comparative cost drivers such as devices, consumables, replacement frequency, training and service delivery requirements.

In addition, analyses of global insulin prices were used to contextualize the resource implications of different insulin regimens, recognizing substantial variation in prices, procurement mechanisms and affordability across countries and income settings. Economic evidence was summarized and presented to the GDG to inform EtD judgements on resource implications, feasibility and equity alongside evidence on effectiveness.

2.6 Certainty assessment and grading of the evidence

The certainty of the evidence for each critical and important outcome was assessed using the GRADE approach *(27).* For questions addressing the effects of interventions, RCTs were initially rated as high-certainty evidence and observational studies as low-certainty evidence. The certainty of the evidence was then rated down or up based on prespecified GRADE domains, including risk of bias, inconsistency, indirectness, imprecision and publication bias (Table 2).

Table 2. GRADE domains for rating certainty of evidence

Certainty criteria	Definition
Risk of bias	Limitations in the design or conduct of the included studies that may reduce confidence in the estimated effects, such as lack of allocation concealment, inadequate blinding, high loss to follow-up or selective outcome reporting.
Inconsistency	Unexplained variability in the magnitude or direction of effects across studies addressing the same question, reflected by differences in point estimates, minimal or no overlap of confidence intervals or statistical heterogeneity.
Indirectness	Differences between the population, intervention, comparator or outcomes studied and those specified in the PICO question, including concerns about applicability to the target population or to low-resource or humanitarian settings.
Imprecision	Imprecision was assessed by examining the width of confidence intervals in relation to clinically important effect thresholds. In some reviews, a minimal clinically important difference (MCID) approach was applied. In others, imprecision was judged using conventional GRADE criteria based on confidence intervals, sample size and number of events.

Certainty criteria	Definition
Publication bias	The possibility that the available evidence does not represent all relevant studies because of selective publication or selective reporting of outcomes, particularly when evidence is derived from small or industry-sponsored studies.

For diagnostic and classification questions, the certainty of evidence was assessed using GRADE principles adapted for diagnostic accuracy studies. Judgements considered study limitations, applicability to the target population, consistency of results across studies and the precision of diagnostic performance estimates, with particular attention to relevance across different health system contexts.
The evidence synthesis teams prepared GRADE evidence profiles (Web Annex A) for each PICO question, presenting effect estimates and certainty ratings for all critical and important outcomes. These materials were reviewed by the independent guideline methodologist and provided to the GDG in advance of recommendation formulation.

During GDG meetings, the certainty ratings were discussed alongside other EtD domains *(28)*. The GDG reviewed and, where necessary, refined the GRADE judgements to ensure internal consistency across outcomes and PICOs, with particular attention to contextual factors affecting interpretation of the evidence. The final certainty of evidence ratings informed both the direction and strength of recommendations and are presented alongside each recommendation in Chapter 3.

Table 3. GRADE certainty of evidence ratings

Certainty level	Interpretation
High	The GDG is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The GDG is moderately confident in the effect estimate; the true effect is likely to be close to the estimate but may be substantially different.
Low	The GDG has limited confidence in the effect estimate; the true effect may be substantially different from the estimate.
Very low	The GDG has very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate.

2.7 Evidence-to-Decision (EtD) framework

Recommendations were informed by the EtD framework, which provides a structured and transparent approach to moving from evidence to recommendations. The framework was applied to each priority question to support systematic consideration of evidence and contextual factors relevant to adults with type 1 diabetes across diverse health system settings.

During GDG meetings, the methodologist, with assistance from the chairs, guided discussions across the following domains: balance of benefits and harms, certainty of the evidence, values and preferences, resource implications (including cost-effectiveness), equity, acceptability and feasibility. The GDG considered these domains explicitly and documented its judgements to ensure transparency and consistency across recommendations.

Resource implications were considered using available economic evidence, including cost and price analyses for insulin products, delivery devices and monitoring approaches, recognizing substantial variation in affordability and availability across settings. Equity considerations focused on the potential impact of recommendations on access to essential insulin and monitoring technologies, particularly for populations facing structural, geographic or economic barriers to care.

The EtD framework supported the GDG in making explicit, structured judgements and in identifying areas of uncertainty or variability that influenced the direction and strength of recommendations. All EtD judgements were recorded to provide a transparent rationale for recommendations and accompanying remarks.

Table 4. EtD domains considered in recommendation development

EtD domain	Description
Benefits and harms	Assessment of the desirable and undesirable effects of an intervention based on the best available evidence.
Certainty of evidence	Degree of confidence in effect estimates, as assessed using the GRADE approach.
Values and preferences	Importance placed on outcomes by people with type 1 diabetes and variability in these values across populations.
Resource implications	Considerations of costs, affordability and economic impact at patient and health system levels and cost-effectiveness.
Equity	Potential effects on health equity, including access to insulin and monitoring technologies in underserved or vulnerable populations.
Acceptability	Acceptability of interventions to people with type 1 diabetes, health-care providers and health systems.
Feasibility	Practicality of implementation given infrastructure, workforce, training and supply-chain considerations.

2.8 Formulation of recommendations

Draft recommendations were formulated during the second in-person GDG meeting held on 1–4 December 2025. For each PICO question, the GDG considered whether or not to make a recommendation, the direction of the recommendation (for or against the intervention) and its strength, drawing on the totality of evidence and judgements across the EtD domains (Annex 4).

Subsequent meetings held virtually on 4 and 12 March 2026 focused on an outstanding PICO question. During these meetings, the GDG also discussed accompanying remarks and implementation considerations, and reached consensus on the final set of recommendations. Consensus was achieved through structured discussion, facilitated by the guideline methodologist, with the GDG reviewing and approving the final wording, direction and strength of each recommendation. Where consensus could not be reached, decisions were made by vote with 60% threshold agreed by the GDG at the outset of the meeting.

Strong recommendations were made when the GDG judged that the desirable effects of an intervention clearly outweighed the undesirable effects (or vice versa), supported by higher certainty of evidence and consistent judgements across EtD domains, including values and preferences, resource implications, equity, acceptability and feasibility.

Conditional recommendations were made when the GDG concluded that the desirable effects probably outweighed the undesirable effects, but where there was lower certainty of evidence or important uncertainty or variability across EtD domains, such as differences in resource availability, feasibility, equity considerations or contextual applicability across settings. In such cases, recommendations were accompanied by key remarks to support context-specific decision-making and implementation.

The implications of strong and conditional recommendations differ for people with type 1 diabetes, health-care providers and policy-makers, as summarized in Table 5.

Table 5. Interpretation of recommendation strength

Strength of recommendation	Implications
Strong recommendation	Most people in this situation would want the recommended course of action and only a small proportion would not. Health-care providers should generally offer the recommended intervention. Policy-makers can adopt the recommendation as policy in most settings.
Conditional recommendation	Many people would want the recommended course of action, but a substantial proportion would not. Health-care providers should support shared decision-making, recognizing that different choices may be appropriate for different individuals and contexts. Policy-makers may need to consider contextual factors before adopting the recommendation as policy.

2.9 External review and approval

The draft guideline underwent external peer review in April 2026. An ERG, convened by WHO, comprised independent experts with relevant clinical, public health, health-systems and implementation expertise in type 1 diabetes care. ERG members were selected to complement the expertise of the GDG and to ensure balanced geographic and disciplinary representation.

External reviewers provided structured comments on the interpretation of the evidence, the clarity and wording of recommendations and the feasibility and applicability of the guidance. All comments received were collated and systematically reviewed by the WHO Steering Group, in consultation with the independent guideline methodologist. Where appropriate, revisions were made to the guideline text, recommendations and accompanying remarks, while responsibility for final decisions on recommendations remained with the GDG.

Following incorporation of external review feedback and final editorial revisions, the guideline was submitted to the WHO GRC for final assessment. The GRC reviewed the guideline for compliance with WHO methodological standards and approved the guideline prior to publication.



3 Evidence and recommendations



Each recommendation in this guideline is presented together with key information to support interpretation and use in practice. For each recommendation, readers will find:

- a recommendation statement, indicating the direction (for or against an intervention) and its strength (strong or conditional);
- remarks;
- a summary of the evidence; and
- a rationale for judgement.

Remarks

Remarks accompany recommendations where additional explanation or context is required to support appropriate interpretation and implementation.

Remarks may:

- clarify how the recommendation should be applied in practice, including considerations related to dosing, monitoring, training requirements or service delivery;
- highlight important implementation considerations, such as feasibility constraints, resource availability or system-level requirements;
- address contextual factors, including applicability in low-resource, emergency or humanitarian settings;
- identify subgroups or situations where additional caution, flexibility or individualized decision-making may be required; and
- note evidence gaps or areas of uncertainty relevant to interpretation.

Remarks do not change the direction or strength of a recommendation but provide essential guidance to support safe, effective and context-appropriate use.

Summary of the evidence

This subsection summarizes the key findings from the systematic reviews and evidence syntheses that informed the judgements of the GDG. It typically includes:

- Characteristics of the evidence, such as the number and type of studies, sample size (where relevant) and the countries or settings in which studies were conducted, including income classification where applicable.
- Quantitative synthesis of benefits and harms of the intervention by comparator, focusing on outcomes prioritized by the GDG as critical or important for decision-making. This includes effect estimates and the certainty of the evidence assessed using the GRADE approach.
- When data for a specific outcome or time point are not presented, this indicates that such information was not reported in the available evidence.

Implementation-relevant information was summarized where reported. Where qualitative evidence specific to adults with type 1 diabetes was limited, this was noted, and implementation considerations were informed by findings reported in included studies and by GDG expertise.

Rationale for judgements

The section explains how the GDG interpreted the available evidence and contextual considerations when formulating each recommendation. It focuses on the reasoning underpinning the direction and strength of the recommendation, rather than restating evidence summaries.

For each recommendation, the rationale reflects the GDG's judgements on:

- the balance between desirable and undesirable effects, including the size and clinical importance of benefits and harms;
- the certainty of the evidence, as assessed using the GRADE approach; and
- contextual considerations drawn from the EtD framework, including values and preferences, resource implications, equity, acceptability and feasibility.

For EtD domains where evidence was limited, particularly values and preferences, acceptability and feasibility specific to adults with type 1 diabetes, judgements were informed by information reported in the included studies and by the GDG expertise. This included perspectives from members with type 1 diabetes.

The rationale presented alongside each recommendation summarizes how evidence and EtD considerations informed its direction and strength.

Table 6. Summary of recommendations

Category	No	Recommendation
Diagnosis and classification	**1**	Consider diabetes-specific biomarkers, such as pancreatic islet cell autoantibodies and serum/plasma C-peptide, when a diagnosis of type 1 diabetes in adults is uncertain. *(conditional recommendation, very low certainty)*
Insulin use	**2a**	Use intensified insulin therapy (multiple daily injections with dose adjustment to blood glucose values) for adults with type 1 diabetes. *(strong recommendation, moderate certainty)*
	2b	Consider intensified insulin therapy for adults with type 1 diabetes in emergency and humanitarian settings. *(conditional recommendation, low certainty)*
	3a	Either human insulin or insulin analogues can be used as bolus insulin. Human insulin is the preferred option because it is in general less costly. *(conditional recommendation, moderate certainty)*
	3b	Consider ultra rapid-acting insulin analogues as bolus insulin at mealtimes or after meals for adults with type 1 diabetes. *(conditional recommendation, very low certainty)*
	4a	Either human insulin or insulin analogues can be used as basal insulin. Human insulin is the preferred option because it is in general less costly. *(conditional recommendation, moderate certainty)*
	4b	Consider once-daily long-acting insulin analogues at the time of day preferred by the adult with type 1 diabetes. *(conditional recommendation, low certainty)*
	5	Consider premixed human insulin or self-mixed human insulin (NPH and regular human insulin drawn from separate vials or injected from separate pens) for adults with type 1 diabetes. *(conditional recommendation, very low certainty)*
Insulin delivery	**6**	Consider pens over syringes to deliver insulin in adults with type 1 diabetes. *(conditional recommendation, very low certainty)*
Clinical monitoring of glycaemic control	**7**	Offer HbA1c testing at up to three-monthly intervals to adults with type 1 diabetes. *(conditional recommendation, low certainty)*
	8	Aim to achieve an HbA1c of ≤ 7.0% (53 mmol/mol) in most adults with type 1 diabetes. *(conditional recommendation, moderate certainty)*

Category	No	Recommendation
Self-monitoring of glycaemia	**9**	Consider self-monitoring by fingerstick testing, real-time continuous glucose monitoring (rtCGM) or intermittently scanned (flash) continuous glucose monitoring (isCGM) in adults with type 1 diabetes. *(conditional recommendation, moderate certainty)*
	10	Consider frequent self-monitoring of blood glucose in adults with type 1 diabetes, three or more times per day. *(conditional recommendation, very low certainty)*
	11	Consider urine glucose testing in adults with type 1 diabetes when blood glucose testing is not available for self-monitoring. *(conditional recommendation, low certainty)*

Interpretation of recommendation

- **"Use"** is for the strong recommendation, reflecting the GDG's confidence that desirable effects clearly outweigh undesirable effects across most contexts and populations.
- **"Consider"** is for most conditional recommendations, to indicate that the option is acceptable and appropriate for some, but not all, adults with type 1 diabetes, depending on individual circumstances, values, preferences or context.
- **"Either"** indicates that both options are acceptable, with the preferred option and the reason for the preference stated in the recommendation.
- **"Offer"** indicates that, as part of shared decision-making, health-care providers inform patients of the test, advise them of its utility in guiding optimal routine care and encourage them to test.
- **"Aim to achieve"** indicates a general treatment target for most adults, to be individualized based on clinical judgement.

Strength (strong or conditional) and certainty of the evidence (high, moderate, low or very low) are stated alongside every recommendation and should be read together with the wording above (see Section 2.8).

3.1 Diagnosis and reclassification of type 1 diabetes

Diagnosis of type 1 diabetes

Recommendation 1

Consider diabetes-specific biomarkers, such as pancreatic islet cell autoantibodies and serum/plasma C-peptide, when a diagnosis of type 1 diabetes in adults is uncertain.
(conditional recommendation, very low certainty)

Remarks

- The diagnosis of type 1 diabetes is usually based on characteristic symptoms (e.g. thirst, frequent urination, blurred vision, fatigue) and signs (unintentional weight loss, signs of ketoacidosis), with diagnostic tests (plasma glucose, with or without measurement of ketonaemia and metabolic acidosis).
- Biomarker testing supports clinical judgement when the diagnosis of type 1 diabetes in adults is uncertain and should not delay initiation of insulin when clinically indicated.
- Biomarkers include serum/plasma C-peptide, glutamic acid decarboxylase (GAD) antibodies, islet antigen-2 antibodies (IA-2A), insulin autoantibodies (IAA), islet cell antibodies (ICA) and zinc transporter 8 autoantibodies (ZnT8A) or in combinations.
- Availability and feasibility of biomarker testing in many settings, including low-resource, emergency and humanitarian contexts, may be limited, but lack of access to biomarkers should not prevent timely diagnosis and management on clinical grounds.
- Biomarker testing may be most useful where diabetes type is unclear or misclassification is suspected, and where results are likely to influence ongoing clinical management.
- Introduction of insulin treatment is conditional on metabolic features, not on biomarker test results.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

A total of 14 non-randomized studies were included and formed the basis of the evidence synthesis. These studies assessed the diagnostic performance of a range of biomarkers, including C-peptide (plasma and urinary), GAD antibodies, IA-2A, IAA, ICA, ZnT8A and combinations of biomarkers.

The studies included cohort and cross-sectional designs and were conducted across a range of geographic regions, including South-East Asia, Europe, Africa, North America and the Caribbean, and the Middle East and North Africa, reflecting substantial diversity in populations and health system contexts. Participants were adults with diabetes in whom classification remained uncertain. The designs of identified studies were not suitable for assessing diagnostic accuracy.

Across studies, reference standards varied, most commonly relying on clinical diagnosis based on established criteria and/or clinical course (such as insulin dependence or follow-up treatment patterns). The duration of diabetes in each study had a wide range, and there was considerable heterogeneity in index tests, assay methods, thresholds and reference standards, which precluded statistical pooling of results. As a result, findings were narratively synthesized and organized by biomarker type.
See Web Annex A for the summary of included studies.

Outcomes

The evidence primarily reports diagnostic accuracy outcomes, including test sensitivity, test specificity, positive predictive value, negative predictive value and likelihood ratios, where reported. Across all biomarkers, the certainty of the evidence was very low, largely due to study design limitations, indirectness and substantial heterogeneity in assays, thresholds and reference standards.
For C-peptide, studies using serum/plasma or urinary measurements reported wide variability in diagnostic performance, with sensitivity 54–100% and specificity 71–97.6%. Diagnostic accuracy varied markedly across populations and clinical contexts, including special populations such as individuals with kidney failure and subgroups defined by diabetes phenotype.

For islet autoantibodies, performance also varied substantially by biomarkers and assays. GAD antibodies generally showed moderate to high specificity (92–98.5%) with highly variable sensitivity (31–97%), while ZnT8A and IA-2A demonstrated high specificity but low to moderate sensitivity across studies. Evidence for ICA and IAA was limited to a small number of studies and showed variable sensitivity with high specificity. Likelihood ratios, where reported, ranged widely across biomarkers and assays.

Studies evaluating combinations of biomarkers reported high point estimates of diagnostic accuracy in some individual analyses. However, findings were inconsistent across different combinations and thresholds and were based on small numbers of studies, resulting in very low certainty.

Across all biomarkers, evidence was limited to diagnostic accuracy outcomes. No consistent evidence was identified for the impact of biomarker testing on outcomes, including HbA1c, DKA, access to therapies or technologies, quality of life or mortality.

See Web Annex A Tables 1.1–1.7 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Rationale for judgement

The GDG considered biomarker testing relevant when clinical features do not allow confident classification and misclassification may delay appropriate insulin management. Misclassification at diagnosis may lead to inappropriate treatment decisions, with potential implications for timely initiation of appropriate therapy for type 1 diabetes, which differs from that for type 2 diabetes. The GDG noted there was insufficient evidence to indicate which test was the most effective in distinguishing between type 1 diabetes and other types of diabetes, and the recommendation was based on their clinical experience. The GDG agreed that measurement of beta-cell autoantibodies is a clinically validated indicator of immune-mediated beta-cell destruction in people with diabetes.

The GDG noted that published literature shows that the prevalence of autoantibody positivity in people with type 1 diabetes declines with time elapsed since diagnosis thus making autoantibody testing probably more informative around the time of clinical diagnosis of diabetes. Similarly, measurement of serum C-peptide is often used and clinically validated measure of beta-cell function. The serum levels of C-peptide also decline with time elapsed since diagnosis, as destruction of pancreatic beta-cells continues in the natural history of type 1 diabetes. At the time of diagnosis there is typically some preserved endogenous insulin secretion which declines with time, so the test is better at discriminating between type 1 and other types of diabetes the more time has elapsed since the initial diagnosis of diabetes. However, the available evidence shows that the time to absolute insulin deficiency since diabetes diagnosis could be several years and there is too little evidence to recommend a cut-off time point by which absolute insulin deficiency is established in type 1 diabetes.

The GDG judged that the desirable effects of biomarker testing were uncertain. The available evidence was limited to diagnostic accuracy outcomes and did not demonstrate effects on critical and important outcomes. The undesirable effects were judged to be trivial or small, as biomarker testing is minimally invasive and associated with limited direct harm. Despite few reports of test likelihood ratios, the generally high specificity suggests a high positive likelihood ratio. Thus, despite the overall uncertain downstream benefit of testing for biomarkers upfront in suspected type 1 diabetes, biomarker testing can potentially give a confirmatory label to a case with an uncertain diagnosis.

The overall certainty of the evidence was rated as very low, reflecting methodological limitations of the included studies, heterogeneity in index tests, reference standards and thresholds, and the absence of evidence linking biomarker use to the outcomes. As a result, there was substantial uncertainty regarding the benefit.

The GDG judged that there was no important variability in how people value the critical outcomes, as correct diagnosis was considered essential for guiding appropriate treatment decisions. Overall, the GDG concluded that the balance between benefits and harms probably favours the intervention, despite the uncertainty in effect estimates.

Resource requirements were judged to be potentially large, given laboratory requirements with variability in access to laboratory infrastructure, trained personnel and diagnostic supplies across settings noted. The GDG considered that selective biomarker testing in cases of diagnostic uncertainty would probably favour cost-effectiveness compared with routine testing of all adults with diabetes, despite large resource costs.

The potential impact on health equity was judged to vary, as limited access to biomarker testing in low-resource or humanitarian settings could exacerbate existing inequities if not carefully implemented. The GDG judged biomarker testing to be probably acceptable to patients and health-care providers and feasible to implement in settings where appropriate laboratory services are available.

Taking these considerations together, the GDG made a conditional recommendation to consider using biomarkers when the diagnosis of type 1 diabetes in adults is uncertain, reflecting very low certainty of evidence and the need to consider resource availability and contextual factors.

Reclassification of type 1 diabetes

The GDG selected not to generate a recommendation on the use of biomarkers to reclassify diabetes type in adults previously diagnosed with another type of diabetes but clinically suspected of having type 1 diabetes.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

One non-randomized study (Pilla 2018) was identified for this PICO. It is a retrospective secondary analysis of stored blood samples from 12 participants enrolled in the IDeaLS trial, an RCT of adults clinically diagnosed as having type 2 diabetes randomized to medical weight loss or bariatric surgery. Following one participant experiencing postoperative DKA, pre-intervention samples from all participants were analysed retrospectively to assess the diagnostic accuracy of biomarkers in identifying the single individual subsequently reclassified as having type 1 diabetes. Biomarkers assessed included plasma C-peptide (fasting and meal-stimulated), GAD antibodies and ZnT8A. The reference standard incorporated positive islet cell antibodies, a low fasting C-peptide level and persistent insulin requirement after gastric bypass.

Outcomes

Evidence was limited to diagnostic accuracy outcomes. No evidence was identified for outcomes, including HbA1c, prevention of DKA, access to appropriate therapies or technologies, quality of life or mortality.

For plasma C-peptide, sensitivity was 100% across all tested thresholds, with specificity ranging from 73% to 100% depending on the threshold applied. For GAD antibodies, sensitivity was 100% and specificity was 82%. For ZnT8A, both sensitivity and specificity were 100%. Across all three biomarkers, the certainty of the evidence was rated as very low, due to serious risk of bias, indirectness and imprecision, reflecting the single study, very small sample size and the retrospective nature of the analysis applied to identify a single reclassified case.

See Web Annex A Tables 2.1–2.3 for details of the evidence profiles.

Rationale for judgement

The GDG considered biomarker-assisted reclassification to be a clinically important question, recognizing that misclassification of type 1 diabetes as another diabetes type may result in failure to initiate appropriate insulin therapy and increased risk of serious outcomes.

The GDG noted that, in practice, biomarker testing may still be warranted where type 1 diabetes is clinically suspected in an individual previously diagnosed with another diabetes type, and that the conditional recommendation on biomarker use in diagnostic uncertainty may apply in this context. However, the single eligible study presented a retrospective secondary analysis in which reclassification had already occurred clinically prior to biomarker testing, and diagnostic accuracy estimates derived from a single case within a 12-person study could not be generalized. The GDG concluded that the available evidence was insufficient to support a separate recommendation on reclassification and identified this as a research gap.

3.2 Insulin therapy for people with type 1 diabetes

3.2.1 Insulin regimens

Recommendation 2a

- Use intensified insulin therapy (multiple daily injections with dose adjustment to blood glucose values) for adults with type 1 diabetes.
  (strong recommendation, moderate certainty)

Remarks

- Intensified insulin therapy refers to a regimen of three or more injections per day comprising a basal insulin and mealtime bolus doses, with adjustment of doses based on self-monitored blood glucose values, carbohydrate intake and physical activity.

- Regular blood glucose monitoring is integral to the safe and effective use of intensified therapy. Access to monitoring should be ensured alongside initiation of intensified regimens, and adults should receive education on how to use blood glucose values to adjust doses.

- Education of individuals with type 1 diabetes is a pre-requisite for empowering them to adjust their insulin dosage, especially in circumstances where access to competent health professionals is limited.

Recommendation 2b

- Consider intensified insulin therapy for adults with type 1 diabetes in emergency and humanitarian settings.
  (conditional recommendation, low certainty)

Remarks

- The identified trials defined intensified insulin therapy as a regimen of three or more injections per day comprising a basal insulin and mealtime bolus doses, with adjustment of doses based on self-monitored blood glucose values, carbohydrate intake and physical activity. The identified trials compared one to two daily injections with three or more.

- In settings where supply may be interrupted, health-care providers should have plans for transition to simpler regimens as an interim measure.

- Regular blood glucose monitoring is integral to the safe and effective use of intensified therapy. Access to monitoring should be ensured alongside initiation of intensified regimens, and adults should receive education on how to use blood glucose values and available diet to adjust doses.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

The evidence informing this section was derived from RCTs comparing intensified insulin therapy (multiple daily injections with dose adjustment to blood glucose) with conventional therapy (once or twice daily injections with minimal adjustment) in adults with type 1 diabetes.

The landmark Diabetes Control and Complications Trial (DCCT) was not included in the quantitative evidence synthesis for this comparison because it addressed a different question – whether targeting lower glycaemic levels reduces the risk of complications – rather than whether the intensity of a particular regimen produces better outcomes under none or equivalent glycaemic goals. Nonetheless, the group randomized to achieve lower HbA1c target values in DCCT was treated with multiple insulin injections and the DCCT findings are consistent with the other trials and were taken into account when assessing the certainty of evidence and formulating this recommendation.

Four RCTs compared intensified insulin therapy (three or more injections per day with dose adjustment to blood glucose) with conventional therapy (one to two injections per day with minimal adjustment), with follow-up ranging from 2 to 10 years. Trials were conducted in outpatient specialist diabetes clinics in Sweden, Norway, Italy and Germany. Sample sizes were small, ranging from 30 to 102 participants per trial. The enrolled population comprised adults of both sexes with a mean age ranging from 26 to 38 years, mean diabetes duration of 7 to 21 years, mean HbA1c between 9.4% and 13.1%, and mean body mass index (BMI) between 22 and 26 kg/m^2. No trials were conducted in LMICs or in emergency or humanitarian settings, which substantially limits the applicability of findings to the range of health system contexts to which this guideline applies.

Outcomes

Four RCTs conducted between 1986 and 1996 compared intensified insulin therapy (multiple daily injections with dose adjustment to blood glucose) with conventional therapy (once or twice daily injections with minimal adjustment) in adults with type 1 diabetes. Trials were conducted in Sweden (Stockholm Diabetes Intervention Study), Norway (Oslo Study), Italy (Verillo) and Germany (Linn), with follow-up ranging from 2 to 10 years. Sample sizes were small, ranging from 30 to 102 participants per trial. No trials were conducted in humanitarian settings.

For glycaemic control, intensified therapy was associated with a clinically important reduction in HbA1c compared with conventional therapy (mean difference (MD) -1.17%, 95% confidence interval (CI) -1.47 to -0.87), exceeding the pre-specified MCID of 0.5%. Fasting blood glucose was also lower in one trial providing data at two years (MD -2.4 mmol/L, 95% CI -2.91 to -1.89). Both outcomes were rated as low certainty, due to risk of bias from the inability to blind participants or providers to regimen assignment, and imprecision.

For hypoglycaemia, the evidence was uncertain across all subtypes. All hypoglycaemia, measured as the proportion of blood glucose values below predefined thresholds, was higher with intensified therapy. In one study, at 6 months, the proportion of values below 2.5 mmol/L was higher with intensified therapy, but the confidence interval crossed zero, indicating the result is also compatible with no difference (MD 1.0 percentage points, 95% CI -1.77 to 3.77). In another study, at 5 years, the proportion of values below 3.5 mmol/L was higher (MD 1.7 percentage points, 95% CI 1.34 to 2.06). Severe hypoglycaemia appeared in more people receiving intensified therapy (relative risk (RR) 1.16, 95% CI 0.95 to 1.42), corresponding to approximately 67 more people per 1000. Nocturnal hypoglycaemia was not reported. All hypoglycaemia outcomes were rated as very low certainty.

For DKA, two trials provided data, few people experienced the complication (1 versus 4) and the estimate showed serious imprecision (RR 0.28, 95% CI 0.03 to 2.40), rated as low certainty. For all-cause mortality, one trial reported four versus three people died at 10 years (RR 1.50, 95% CI 0.35 to 6.37), also rated as low certainty.

For microvascular complications, intensified therapy was associated with a large and statistically significant reduction in nephropathy (RR 0.26, 95% CI 0.08 to 0.84; low certainty), corresponding to approximately 144 fewer cases per 1000. Neuropathy was also reduced with intensified therapy in two trials (RR 0.36, 95% CI 0.16 to 0.77; low certainty). Retinopathy showed a possible reduction but with a wide confidence interval that included both benefit and harm (RR 0.76, 95% CI 0.33 to 1.73; very low certainty). Macrovascular outcomes were not reported in any trials.

Body weight gain was higher with intensified therapy in two trials (MD 2.6 kg, 95% CI 2.21 to 2.99; low certainty). Quality of life was not reported.

Overall, the certainty of evidence for this comparison ranged from very low to low. Key limitations included the risk of bias across all included trials, small sample sizes and imprecision in rare outcomes.

See Web Annex A Table 3.1 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Rationale for judgement

The GDG considered regimen intensity for adults with type 1 diabetes to be a priority issue.

The GDG judged that the desirable effects of intensified insulin therapy compared with conventional therapy are large to moderate. Intensified therapy was associated with a clinically meaningful reduction in HbA1c, the only comparison across this PICO where a benefit exceeding the pre-specified MCID was identified, as well as reductions in nephropathy and neuropathy over longer-term follow-up. The GDG noted that, while this evidence is derived from trials conducted in the 1980s and 1990s, the consistency and direction of effects across outcomes were considered biologically plausible and clinically meaningful.

The undesirable effects of intensified therapy were judged to be small. A higher proportion of people receiving intensified therapy experienced hypoglycaemia, though estimates for severe hypoglycaemia were imprecise and uncertain. A possible increase in mortality was identified in a single small trial with very few deaths and was not considered reliable. Weight gain was also higher with intensified therapy in two trials, though certainty was low and the clinical significance in the context of overall benefit was judged to be limited. The GDG noted that the risk of hypoglycaemia is substantially influenced by education on glucose self-monitoring, diet and physical activity and adjustment of insulin dosage accordingly, rather than by regimen intensity alone.

The overall certainty of the direct and indirect evidence was rated as moderate, reflecting consistent directional findings alongside important limitations, including risk of bias in all included trials and imprecision for rare outcomes. There was no evidence from humanitarian settings in which there is usually substantial uncertainty over access to insulin, blood glucose self-monitoring and dietary choices.

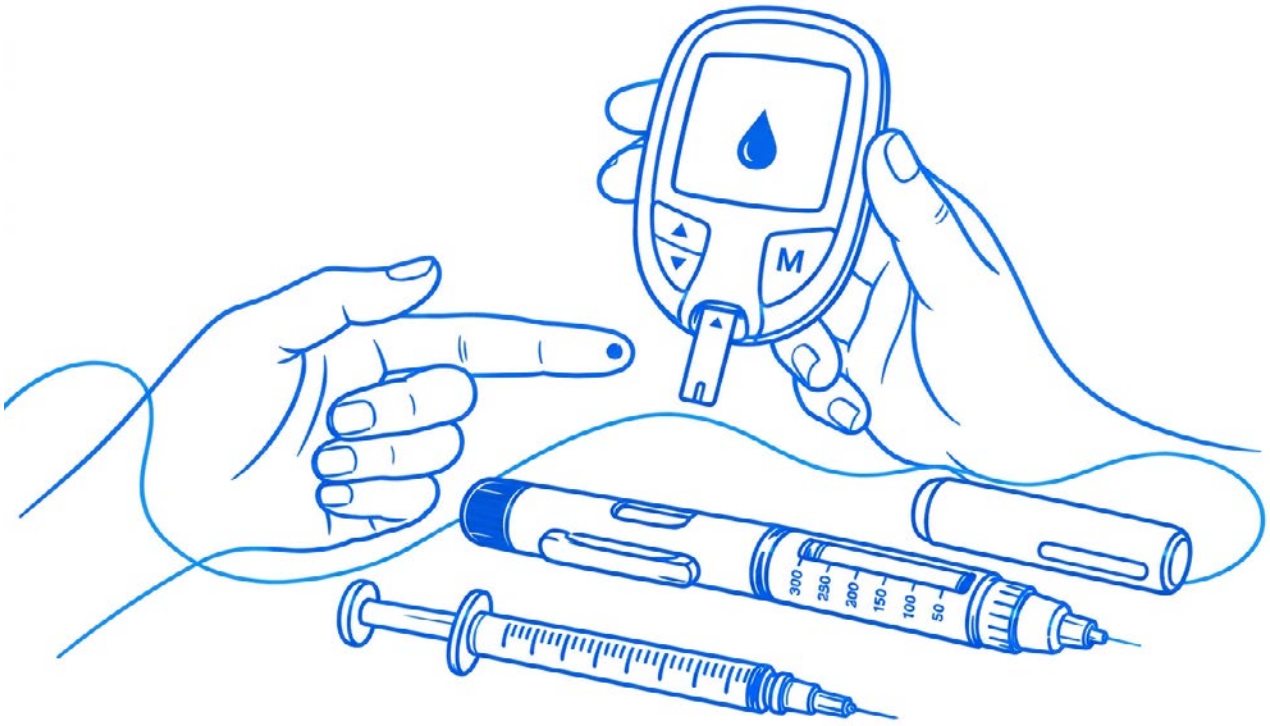
The GDG judged that there was possibly important to probably no important uncertainty or variability in how adults with type 1 diabetes value the critical outcomes. Prevention of long-term complications and better glycaemic control were considered highly valued. Some variability was acknowledged, as the higher injection burden and hypoglycaemia risk associated with intensified therapy may affect the preferences of some individuals.

The balance of benefits and harms was judged to favour intensified therapy. Resource requirements were judged to involve moderate costs. Intensified therapy necessitates more syringes per day and increases the likelihood of use of pen devices and cartridges, further increasing costs. More frequent blood glucose monitoring and greater resources for education of both health-care workers and patients are also required compared with conventional regimens. No formal cost-effectiveness evidence was available. However, it can be argued that better glycaemic control with intensified regimens could result in fewer or delayed long-term complications, making them more cost-effective than conventional regimens.

The impact on health equity was judged to be reduced. Equity may be diminished where access to additional devices and increased monitoring is limited, particularly in settings where patients pay out of pocket. Acceptability to adults with type 1 diabetes was judged as possibly acceptable, given that the higher injection burden and hypoglycaemia risk may reduce acceptability for some individuals. Health-care providers were judged to find intensified therapy highly acceptable where resources are available.

Feasibility was judged to be high where resources are available, but highly dependent on access to insulin and required technologies and on the capacity of health systems to build health-care worker competence. The GDG noted that feasibility may be substantially reduced in emergency and humanitarian settings.

Overall, the GDG issued a strong recommendation in favour of intensified insulin therapy for adults with type 1 diabetes in general settings, reflecting large to moderate benefits, small harms and low certainty of evidence. The GDG issued a separate conditional recommendation for emergency and humanitarian settings, reflecting the reduced feasibility and increased implementation challenges in those contexts. Other possible insulin regimens, such as short- or rapid-acting insulin only or basal insulin only, are unusual and not generally recommended, but could be the only option in humanitarian crises where the type and quantity of insulin is limited, and food availability is uncertain. GDG members have witnessed situations where basal insulin was the only insulin available. Historically, until the formulation of long-acting insulin in the 1930s, treatment consisted of multiple injections of regular insulin. Observational studies described beneficial effects of multiple injections of regular insulin on survival and late complications compared with long-acting insulin. However, no trials of the differences in impact of these approaches were identified.



3.2.2 Short-acting, rapid-acting and ultra rapid-acting (bolus) insulins

Recommendation 3a

- Either human insulin or insulin analogues can be used as bolus insulin. Human insulin is the preferred option because it is in general less costly.
  (conditional recommendation, moderate certainty)

Remarks

- Human insulin used as bolus insulin is referred to as regular or soluble human insulin, while insulin analogues used as bolus insulin include rapid- and ultra rapid-acting insulin analogues.
- Regular human insulin is an effective and appropriate choice for bolus insulin therapy in adults with type 1 diabetes, including low-resource, emergency and humanitarian settings.
- When prescribing regular human insulin, health-care providers should discuss the risk of hypoglycaemia with adults with type 1 diabetes and provide appropriate education on timing of injections in relation to meals, dose adjustment and recognition and management of hypoglycaemia.
- Health-care providers should also discuss the risk of hypoglycaemia when prescribing insulin analogues as bolus insulin.
- Specifically, insulin aspart may be considered for adults with type 1 diabetes who experience frequent severe nocturnal hypoglycaemia, when this persists despite appropriate use of regular human insulin.
- Evidence suggesting a reduction in severe nocturnal hypoglycaemia compared with regular human insulin was observed only for insulin aspart and evidence is insufficient to support a similar effect consistently across all rapid-acting insulin analogues.
- Before switching to a rapid-acting insulin analogue, health-care providers should assess and address potentially preventable causes of hypoglycaemia, including insulin dosing errors, missed or delayed meals, alcohol use, intercurrent illness, inadequate diabetes education or limited access to glucose monitoring.
- Given the substantial cost and modest benefits at best compared to human insulin, decisions to use rapid-acting insulin analogues should primarily take into account their affordability to the individual and/or the health system and equity implications, particularly in low-resource or humanitarian settings.

Recommendation 3b

- Consider ultra rapid-acting insulin analogues as bolus insulin at mealtimes or after meals for adults with type 1 diabetes.
  (conditional recommendation, very low certainty)

Remarks

- This recommendation applies only to ultra rapid-acting insulin analogues (faster-acting insulin aspart, ultra rapid lispro). Post-mealtime dosing may be particularly useful when the timing or composition of a meal is uncertain.

Summary of the evidence

Recommendation 3a

Quantitative evidence

Characteristics of the evidence

A total of 15 RCTs compared rapid-acting insulin analogues with regular human insulin, and included head-to-head comparisons between different insulin analogues. Most trials were multicentre studies conducted in outpatient specialist diabetes clinics and enrolled adults with established type 1 diabetes receiving multiple daily injection regimens. Trials were predominantly conducted in high-income settings, with some studies including participants from Asia, South Africa and Latin America. Sample sizes ranged from small crossover studies enrolling fewer than 50 participants to large multicentre trials enrolling more than 700 participants. Follow-up durations ranged from 24 to 52 weeks, limiting the assessment of long-term clinical outcomes.

Interventions included rapid-acting insulin analogues (insulin lispro[2] , insulin aspart[3] and insulin glulisine[4]) and ultra rapid-acting insulin analogues (faster-acting insulin aspart and ultra rapid lispro). Comparators included regular human insulin or other insulin analogues, depending on the study. Outcomes assessed included HbA1c, hypoglycaemia (including severe and nocturnal hypoglycaemia), DKA, adverse events and selected patient-reported outcomes such as treatment satisfaction.



[2] Type of rapid-acting insulin analogue, named after the interchange of lysine and proline at positions B28 and B29.
[3] Type of rapid-acting insulin analogue, named after the substitution of aspartic acid for proline at position B28.
[4] Type of rapid-acting insulin analogue, named after the substitutions of glutamic acid and lysine in the insulin molecule.

Across trials, there was substantial heterogeneity in insulin regimens, background basal insulin, definitions of hypoglycaemia and outcome reporting. While pairwise meta-analyses and network meta-analyses were conducted for some outcomes, imprecision and heterogeneity limited certainty for several estimates.

See Web Annex A for the summary of included studies.

Outcomes

Across randomized trials, rapid-acting insulin analogues were associated with small reductions in HbA1c compared with regular human insulin. Pairwise and network meta-analysis estimates suggested mean HbA1c differences ranging from approximately 0.14% to 0.25% lower with insulin analogue. For example, network estimates showed mean differences of -0.14% for insulin aspart (95% CI -0.21 to -0.06), -0.22% for insulin lispro (95% CI -0.46 to 0.02) and -0.17% for faster-acting insulin aspart (95% CI -0.28 to -0.05), compared with regular human insulin. For glulisine evidence was available only from an indirect network meta-analysis (NMA) estimate (MD -0.21%, 95% CI -0.48 to 0.06; low certainty). In several comparisons, confidence intervals crossed the line of no effect, indicating uncertainty about the magnitude of the benefit. Head-to-head comparisons between different rapid-acting or ultra rapid-acting insulin analogues did not demonstrate clinically important differences in HbA1c. Overall certainty of the evidence for HbA1c outcomes was moderate to high.

Evidence on hypoglycaemia outcomes was limited and imprecise. For severe hypoglycaemia, most comparisons between rapid-acting insulin analogues and regular human insulin showed little or no difference, with wide confidence intervals reflecting few people experiencing events. In network meta-analyses, relative risks for severe hypoglycaemia ranged from approximately 0.79 to 1.54, depending on the analogue, with confidence intervals frequently crossing both benefit and harm. For example, insulin aspart showed an RR of 0.89 (95% CI 0.73 to 1.09), while insulin glulisine showed an RR of 1.54 (95% CI 0.46 to 5.19), compared with regular human insulin. Certainty of evidence for severe hypoglycaemia was low to very low, reflecting few people with events and imprecision. Evidence suggested a reduction in severe nocturnal hypoglycaemia with insulin aspart compared with regular human insulin (RR 0.63, 95% CI 0.46 to 0.88) with moderate certainty. For non-severe hypoglycaemia, pooled estimates did not demonstrate consistent or clinically important differences between insulin types, with relative risks generally close to 1.0 and wide confidence intervals.

Events of DKA and mortality were limited across trials. Estimates were highly imprecise, with very few people experiencing events and wide confidence intervals. No consistent differences between insulin types were identified for these outcomes, and the certainty of evidence was low to very low.
Reported adverse events were generally infrequent and similar across intervention groups. Serious adverse events were uncommon, and no consistent safety signals were identified for any insulin type.

For aspart, treatment satisfaction, measured by the Diabetes Treatment Satisfaction Questionnaire, was higher than with regular human insulin (MD 2.3, 95% CI 1.32 to 3.28; low certainty). For lispro, Short Form Health Survey-36 physical and mental health scores showed no meaningful difference (moderate

certainty). However, these outcomes were inconsistently reported, often based on a single trial and subject to risk of bias. No evidence was identified for long-term outcomes such as microvascular or macrovascular complications.

Overall, the certainty of the evidence ranged from very low to high across outcomes and insulin analogues, with limitations related to short follow-up duration, imprecision for rare outcomes, heterogeneity in outcome definitions and indirectness for long-term outcomes.

See Web Annex A Tables 4.1–4.5 for details of the evidence profiles.

Economic evidence

Characteristics of the evidence

The economic evidence comparing rapid-acting insulin analogues with regular human insulin in adults with type 1 diabetes comprised 12 economic evaluations, including 11 cost-effectiveness analyses (CEA) and 1 cost-benefit analysis (CBA).

For insulin lispro versus regular human insulin, 6 studies were identified (5 CEA and 1 CBA). These studies were conducted in high-income countries (Canada, Germany, United Kingdom of Great Britain and Northern Ireland, and Australia) and upper-middle-income countries (Brazil and Colombia). Perspectives included the health-care system, health-care payer, insurance and patient. Time horizons ranged from short-term decision-tree models to longer-term modelling incorporating hypoglycaemia and diabetes-related complications. Funding sources included both public funders and the pharmaceutical industry.

For insulin aspart versus regular human insulin, 4 cost-effectiveness analyses were identified. These studies were conducted in Canada, Brazil, Colombia and Iran (Islamic Republic of), predominantly from health-care system or payer perspectives. Modelling approaches included decision-tree and cohort-based models, with clinical inputs derived largely from trial data and published literature.

One additional study compared insulin aspart with insulin lispro, and one study compared rapid-acting insulin aspart with conventional insulin aspart. Both were model-based CEA conducted in upper-middle-income (Colombia) and high-income (United Kingdom of Great Britain and Northern Ireland) settings, respectively. Across studies, reductions in hypoglycaemia, particularly severe or nocturnal hypoglycaemia, were the main drivers of projected health benefits and cost-effectiveness. Assumptions regarding hypoglycaemia rates, acquisition costs and time horizon were key sources of variability. Most studies reported deterministic sensitivity analyses, and several included probabilistic sensitivity analyses, generally showing robustness of base-case findings. No economic evaluations were identified from low-income countries, humanitarian or emergency settings.

Outcomes

In some modelling analyses, the economic evidence suggested that rapid-acting insulin analogues could be cost-effective. However, these results depended largely on assumptions regarding reductions in hypoglycaemia and long-term complications, while the acquisition costs of insulin analogues were substantially higher than those of regular human insulin. In addition, a substantial proportion of studies were funded by manufacturers and conducted primarily in high- and upper-middle-income countries, which limits confidence in the generalizability of these findings across diverse health system settings.

Across the identified economic evaluations, several model-based studies evaluated the cost-effectiveness of rapid-acting insulin analogues compared with regular human insulin using country-specific WTP thresholds.

For insulin lispro versus regular human insulin, three studies found insulin lispro to be cost-effective. Two studies reported incremental cost-utility ratio (ICUR) ranging from US$ 7 382 to US$ 34 769 per quality-adjusted life year (QALY) gained, while one study reported an incremental cost-effectiveness ratio (ICER) of approximately US$ 7 844 per additional 1% reduction in HbA1c. Two further studies reported insulin lispro to be dominant (more effective and less costly). The CBA conducted from a patient perspective in Australia reported net cost savings, favouring insulin lispro.

For insulin aspart versus regular human insulin, two studies reported ICERs well below country-specific thresholds, including estimates of US$ 2 057 per additional 1% reduction in HbA1c and approximately US$ 88 per additional 1% reduction in HbA1c, while two other studies reported insulin aspart to be dominant. Probabilistic sensitivity analyses, when conducted, indicated a greater than 50% probability of cost-effectiveness.

In single-model-based studies, insulin aspart was dominant over insulin lispro, and faster-acting insulin aspart was dominant over conventional insulin aspart. These findings remained unchanged in sensitivity analyses, but each comparison was informed by a single study.

See Web Annex B Table 1 for details of the economic studies.

Recommendation 3b

Characteristics of the evidence

Three RCTs contributed data to the evidence profile for this comparison. Most trials were conducted in outpatient specialist diabetes clinics. The enrolled population comprised adults of both sexes with a mean age ranging from 41 to 46 years, a mean HbA1c between 7.3% and 7.6%, and a mean BMI between 25 and 27 kg/m^2. Trials were conducted across multiple high-income countries. No trials were conducted exclusively in LMICs or in emergency or humanitarian settings, which substantially limits the applicability of the findings to the range of health system contexts covered by this guideline.

Outcomes

Three RCTs (ONSET 1, ONSET 8, PRONTO T1D) compared mealtime with post-mealtime administration of ultra rapid-acting bolus insulin in adults on multiple daily injection regimens, over 26 weeks, across multiple high-income settings.

HbA1c was equivalent between mealtime and post-mealtime dosing (MD -0.17%, 95% CI -0.25 to -0.09; high certainty), with the difference well below the pre-specified MCID of 0.5%, indicating no clinically important difference. All incident hypoglycaemia showed no important difference between mealtime and post-mealtime administration (RR 1.00, 95% CI 0.98 to 1.03; moderate certainty). Severe hypoglycaemia showed no important difference (RR 1.00, 95% CI 0.95 to 1.05; very low certainty). All nocturnal hypoglycaemia showed a possible increase with mealtime dosing (RR 1.11, 95% CI 1.00 to 1.24; very low certainty), but the results were inconsistent across trials. Severe nocturnal hypoglycaemia and adherence to treatment showed no important differences (very low certainty for each). DKA was rare,

with numerically more events in the mealtime arm in one trial (very low certainty). All-cause mortality was rare across trials (very low certainty). Macrovascular and microvascular complications were reported but extremely rare, with very low certainty for all outcomes.

Quality of life was assessed using the 36-Item Short Form Health Survey in one trial. The physical component score was higher with post-mealtime dosing (MD -1.21, 95% CI -2.35 to -0.07; high certainty). The mental component score showed no statistically significant difference (MD 0.22, 95% CI -1.09 to 1.53; high certainty). Body weight change showed no statistically significant difference between groups (MD -0.61 kg, 95% CI -3.41 to 2.19; moderate certainty). Overall, certainty of evidence was high for HbA1c equivalence and quality of life, moderate for any hypoglycaemia and body weight change, and very low for severe hypoglycaemia and most other outcomes.

See Web Annex A Table 3.2 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Rationale for judgement

Type of bolus insulin

The GDG considered the choice of bolus insulin for adults with type 1 diabetes to be a priority issue.

In 2018, WHO recommended the use of human insulin to manage blood glucose in adults with type 1 diabetes (strong recommendation, low-quality evidence), including both short-acting (regular human insulin) and intermediate-acting (NPH insulin) human insulin. That recommendation was based on the absence of evidence demonstrating superior effectiveness of insulin analogues and the more favourable resource-use profile of human insulin. Since that time, additional randomized and economic evidence comparing rapid-acting insulin analogues with regular human insulin has become available. The GDG therefore re-examined the evidence to determine whether the 2018 recommendation should be updated and whether rapid-acting insulin analogues should be considered in specific clinical circumstances.

The GDG judged that the beneficial effects of rapid-acting insulin analogues compared with regular human insulin are small overall and uncertain for most adults with type 1 diabetes. Randomized trials demonstrated small reductions in HbA1c and no consistent clinically important differences in most outcomes. For severe hypoglycaemia, most comparisons showed little or no difference. However, evidence suggested a reduction in severe nocturnal hypoglycaemia with insulin aspart compared with regular human insulin. This potential benefit was not consistently observed with other rapid-acting insulin analogues. The GDG considered this potential benefit to be modest and uncertain, but possibly meaningful for individuals who experience recurrent severe nocturnal hypoglycaemia. Head-to-head comparisons between different rapid-acting or ultra rapid-acting insulin analogues did not demonstrate clinically important differences across other outcomes.

The undesirable effects of both human insulin and rapid-acting insulin analogues were judged to be trivial or small. Serious adverse events were uncommon across trials, and no consistent safety concerns were identified. The GDG noted that the principal harms were not related to intrinsic drug toxicity, but to hypoglycaemia risk, which is influenced by insulin dosing, timing of meals, diabetes education and access to glucose monitoring rather than insulin type alone.

The overall certainty of the evidence was judged to be moderate, reflecting consistent findings of small effects across randomized trials, alongside limitations, including short follow-up, imprecision for rare outcomes such as severe hypoglycaemia and DKA, heterogeneity in outcome definitions and indirectness for long-term outcomes such as microvascular and macrovascular complications. For nocturnal hypoglycaemia, the certainty of the direct evidence for aspart compared with regular human insulin was moderate.

The GDG judged that values and preferences are likely to vary. Avoiding severe hypoglycaemia is highly valued, particularly among individuals who experience recurrent episodes or nocturnal events. Treatment choices may be influenced by simplicity, predictability, affordability and continuity of access that may support the use of regular human insulin in many settings. The GDG did not identify evidence of large variability in how adults with type 1 diabetes value the outcomes overall but recognized that preferences may differ depending on prior hypoglycaemia experience and local context.

Overall, the balance between benefits and harms was judged to favour regular human insulin as the preferred bolus insulin option for most adults with type 1 diabetes, given its effectiveness, safety and wide availability. Although available evidence showed little or no difference between rapid-acting insulin analogues and regular human insulin for severe hypoglycaemia overall, the GDG agreed that insulin aspart may be considered for adults with frequent nocturnal severe hypoglycaemia (defined as two or more episodes of hypoglycaemia requiring the aid of another person per year) who continue to experience hypoglycaemic episodes despite appropriate use of regular human insulin and after addressing potentially preventable causes.

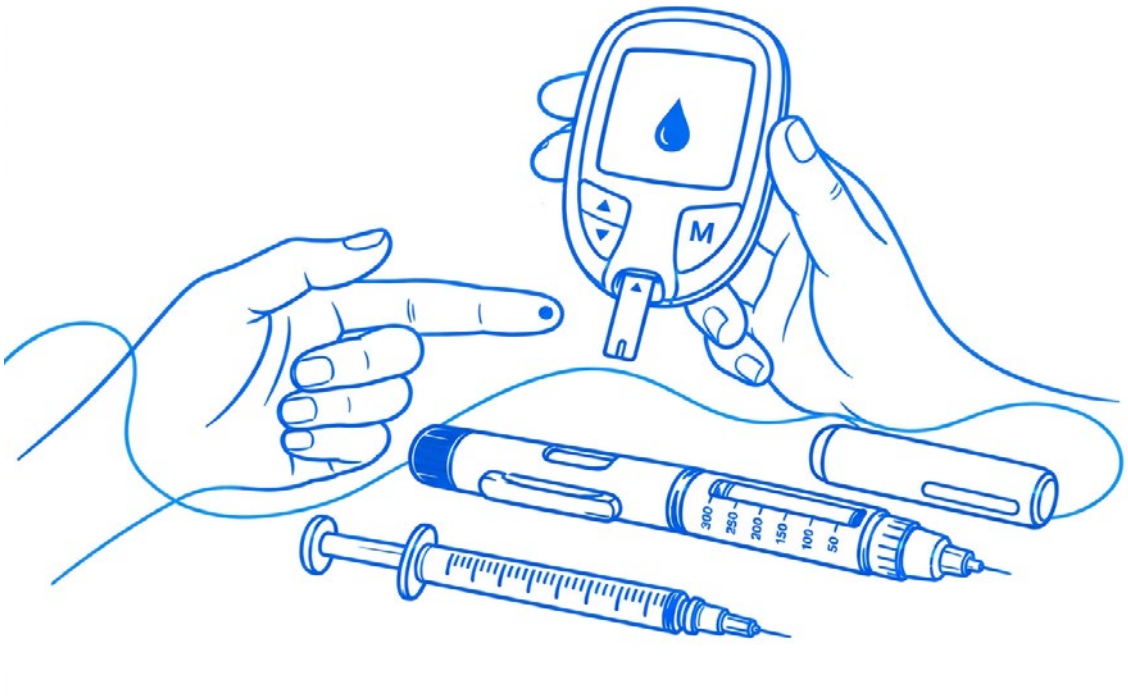
Resource requirements were judged to be large overall but highly variable by country and health system context. Global insulin price analyses reviewed by the GDG indicate that although prices for both human and insulin analogues have declined substantially over the past 15 years, rapid-acting insulin analogues remain consistently more expensive than regular human insulin. In 2025, median retail prices in high and middle-income countries were approximately US$ 2.9 per 100 international unit (IU) for rapid-acting analogues compared with approximately US$ 1.8 per 100 IU for regular human insulin. Therefore, switching from human to analogue bolus regimens was estimated to increase costs by approximately 1.5-fold in high- and upper-middle-income countries and up to 2.8-fold in lower middle-income countries. These cost differentials vary by income setting and may be further amplified by the use of pen-based delivery systems, which can substantially increase total treatment costs across settings.

The GDG noted that economic evaluations, primarily from high-income settings, suggest possible cost-effectiveness under certain assumptions, but concerns regarding model dependence on unsubstantiated or undisclosed assumptions, study funding sources and limited generalizability reduce confidence in broad applicability.

The impact on health equity was judged to vary. Preferential or widespread use of rapid-acting insulin analogues without clear clinical indication could exacerbate inequities in settings with constrained budgets or limited insulin supply. Maintaining regular human insulin as the preferred bolus option supports equitable access and continuity of care across diverse contexts.

Both human insulin and rapid-acting insulin analogues were judged acceptable by people with type 1 diabetes and health-care providers. Feasibility was judged to be high for regular human insulin across all settings, and variable for rapid-acting insulin analogues.

Overall, the GDG issued a conditional recommendation that either human insulin or insulin analogues can be used as bolus insulin for adults with type 1 diabetes, with human insulin as the preferred option because it is in general less costly (moderate certainty).



Timing of bolus insulin

The GDG considered timing of bolus insulin administration for ultra rapid-acting insulin analogues for adults with type 1 diabetes to be a priority issue.

The GDG judged that the desirable effects of post-mealtime compared with mealtime administration were trivial. High-certainty evidence showed no clinically important difference in HbA1c between the two approaches. The GDG noted that high-certainty evidence from one trial showed a small improvement in the physical component of quality of life, favouring post-mealtime dosing. However, as this was an important rather than critical outcome and was based on a single trial, it did not alter the overall judgement of trivial desirable effects.

All hypoglycaemia showed no important difference between the two approaches (moderate certainty). Severe hypoglycaemia similarly showed no important difference (very low certainty). The GDG noted a possible increase in all nocturnal hypoglycaemia with mealtime compared with post-mealtime dosing, though certainty was very low. The undesirable effects were judged to be uncertain because the very low certainty of the evidence for critical safety outcomes precluded meaningful conclusions about harms.

The overall certainty of the evidence was rated as very low, driven by the very low certainty for severe hypoglycaemia and other critical safety outcomes, despite high-certainty evidence of no clinically important difference in HbA1c.

The GDG judged that there was possibly important to probably no important uncertainty or variability in how adults with type 1 diabetes value the critical outcomes.

The balance of benefits and harms was judged not to favour either approach. Resource requirements were judged to involve negligible costs and savings, as the dose is the same regardless of timing, making this a cost-neutral decision. No cost-effectiveness differences were anticipated. The impact on health equity was judged to be none, with the GDG noting that the ability to choose injection timing may increase equity by giving adults greater flexibility in organizing their daily lives. Acceptability was judged to be high and the ability to choose when to inject was considered highly acceptable to adults with type 1 diabetes and very likely acceptable to health-care providers. Feasibility was judged to be high.

The GDG discussed whether a recommendation was warranted, given the very low certainty of evidence for most outcomes. However, the GDG concluded that a conditional recommendation was preferable to no guidance, particularly given the relevance of flexible bolus timing in settings where meal timing is unpredictable. The GDG emphasized that this recommendation applies only to ultra rapid-acting insulin analogues and should not be generalized to regular human insulin or conventional rapid-acting analogues. Overall, the GDG made a conditional recommendation to consider ultra rapid-acting insulin analogues as bolus insulin at mealtimes or after mealtimes for adults with type 1 diabetes.

3.2.3 Intermediate-acting, long-acting and ultra long-acting (basal) insulins

Recommendation 4a

- Either human insulin or insulin analogues can be used as basal insulin. Human insulin is the preferred option because it is in general less costly.
  (conditional recommendation, moderate certainty)

Remarks

- Human insulin used as basal insulin is referred to as NPH or isophane insulin, while insulin analogues used as basal insulin include long-acting and ultra long-acting insulin analogues.
- Human insulin (NPH insulin) is an effective basal insulin choice for adults with type 1 diabetes, including low-resource, emergency and humanitarian settings.
- When prescribing NPH insulin, health-care providers should discuss the risk of hypoglycaemia and provide education on dosing, timing of injections, meal planning, recognition and management of hypoglycaemia, and dose adjustment during illness or changes in routine.
- Health-care providers should also discuss the risk of hypoglycaemia when prescribing insulin analogues as basal insulin.
- Specifically, insulin detemir may be considered for adults with type 1 diabetes who experience frequent severe or nocturnal hypoglycaemia, when this persists despite appropriate use of human insulin.
- Evidence suggesting a reduction in severe or nocturnal hypoglycaemia compared with NPH insulin was observed only for insulin detemir and evidence was insufficient to support a consistent effect across all long-acting insulin analogues.
- Before switching to a long-acting insulin analogue, health-care providers should assess and address potentially preventable causes of hypoglycaemia, including insulin dosing and timing, missed or delayed meals, alcohol use, intercurrent illness, changes in physical activity, access to glucose monitoring and adequacy of diabetes education.
- Decisions to use long-acting insulin analogues should primarily consider affordability to the individual or health system. Other considerations include sustainability of supply and equity implications, particularly in low-resource or humanitarian settings.
- Strengthening diabetes education and access to blood glucose monitoring is essential to optimize the safety and effectiveness of insulin treatment.

Recommendation 4b

- Consider once-daily long-acting insulin analogues at the time of day preferred by the adult with type 1 diabetes.
  (conditional recommendation, low certainty)

Remarks

- The time of day chosen for the basal injection should be kept as consistent as possible from day to day to support predictable insulin action. Adults should receive education on what to do if a dose is delayed or missed.

- Health-care providers should be aware that the evidence does not support one injection timing over another, and clinical practice should reflect individual patient preference and circumstances.

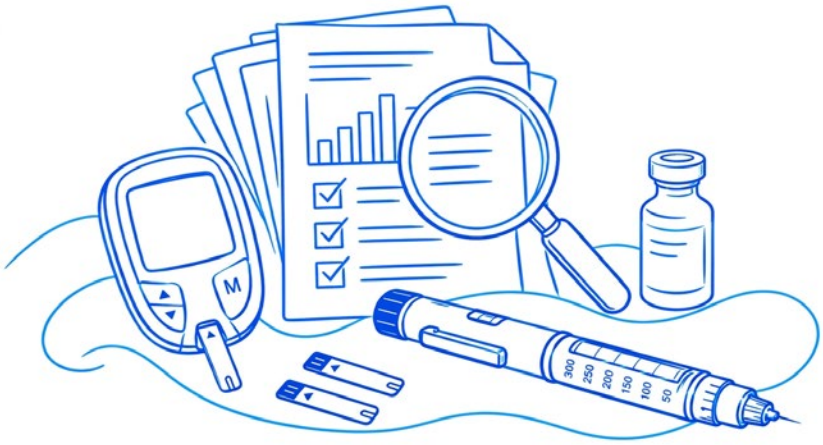
Summary of the evidence

Quantitative evidence

Recommendation 4a

Characteristics of the evidence

A total of 21 RCTs were included in adults with type 1 diabetes, of which 12 compared long-acting insulin analogues (insulin detemir[5] or insulin glargine[6]) with NPH insulin, and included head-to-head comparisons between different insulin analogues. Most trials were multicentre studies conducted in outpatient specialist diabetes clinics and enrolled adults with established type 1 diabetes receiving multiple daily injection regimens. Trials were predominantly conducted in high-income settings, with limited representation from LMICs. Sample sizes ranged from 113 to 749 participants per trial. Follow-up durations ranged from 24 weeks to 24 months, although most outcomes contributing to pooled estimates were reported over approximately 24 to 52 weeks, limiting the assessment of long-term outcomes.



[5] Type of long-acting insulin analogue, named after the deletion of threonine at B30 and attachment of a myristoyl (C14 fatty acid) group to lysine at B29.
[6] Type of long-acting insulin analogue, named after its glycine substitution at A21 and addition of two arginine residues at B31 and B32.

Interventions included long-acting insulin analogues (insulin detemir and insulin glargine), ultra long-acting insulin analogues (insulin degludec[7]) and once-weekly insulin (insulin icodec[8]). Comparators included NPH insulin or basal insulin analogues, depending on the trial. Across trials, there was heterogeneity in basal insulin initiation and titration protocols, background bolus insulin, definitions of hypoglycaemia (including thresholds and ascertainment) and outcome reporting. Pairwise meta-analyses and network meta-analyses were conducted for critical outcomes. Imprecision, heterogeneity and limitations related to open-label trial designs and missing outcome data reduced certainty for several outcomes.

See Web Annex A for the summary of included studies.

Outcomes

Across randomized trials, long-acting insulin analogues did not result in clinically important differences in HbA1c compared with NPH insulin over follow-up periods of approximately 24 to 52 weeks. In network meta-analysis including 19 trials (6897 participants), mean differences in HbA1c were close to zero for all analogues: insulin detemir (MD 0.02%, 95% CI -0.07 to 0.11), insulin glargine (MD 0.01%, 95% CI -0.08 to 0.10), insulin degludec (MD 0.02%, 95% CI -0.11 to 0.15) and insulin icodec (MD 0.17%, 95% CI -0.04 to 0.39). Head-to-head comparisons between long-acting insulin analogues similarly did not demonstrate clinically important differences in HbA1c.

For fasting blood glucose, effects differed across basal insulin analogues. Compared with NPH insulin, insulin detemir results in little or no difference in fasting blood glucose (MD -0.44 mmol/L, 95% CI -0.93 to 0.06; moderate certainty). Evidence on insulin glargine suggests little or no difference in fasting blood glucose compared with NPH insulin (MD -0.76 mmol/L, 95% CI -1.24 to -0.28; low certainty). Insulin degludec reduces fasting blood glucose compared with NPH insulin (MD -1.63 mmol/L, 95% CI -2.30 to -0.96; moderate certainty). For insulin icodec, the evidence suggests little or no difference (MD -0.29 mmol/L, 95% CI -1.50 to 0.29; low certainty).

Evidence on hypoglycaemia was inconsistent and frequently imprecise. For mild or moderate hypoglycaemia, most comparisons between basal insulin analogues and NPH insulin showed little or no difference, with substantial heterogeneity. For example, relative risks were 1.00 (95% CI 0.96 to 1.03) for insulin detemir and 1.00 (95% CI 0.97 to 1.03) for insulin glargine, both with very low certainty. Insulin degludec showed little to no difference (RR 1.01, 95% CI 0.98 to 1.06; low certainty), while insulin icodec may increase mild or moderate hypoglycaemia (RR 1.07, 95% CI 0.99 to 1.16; low certainty).

For severe hypoglycaemia, insulin detemir may reduce the risk of events compared with NPH insulin (RR 0.77, 95% CI 0.59 to 0.99; low certainty). For insulin glargine, insulin degludec and insulin icodec, the evidence was very uncertain, with relative risks ranging from 0.49 to 0.79, suggesting possible reductions, but these estimates are based on very low certainty evidence due to serious risk of bias and imprecision.

For nocturnal hypoglycaemia, insulin detemir may slightly reduce mild or moderate nocturnal hypoglycaemia compared with NPH insulin (RR 0.93, 95% CI 0.87 to 1.00; low certainty), whereas insulin

[7] Type of long-acting insulin analogue, named after the deletion of threonine at B30, addition of a glutamic acid linker and attachment of a hexadecanedioic acid (C16 fatty diacid) side chain to lysine at B29.
[8] Type of once-weekly long-acting insulin analogue, named after its ionic interactions (“ico”) and C20 icosane-derived fatty diacid side chain (“dec”), which together contribute to its prolonged duration of action.

glargine may not reduce nocturnal hypoglycaemia (RR 0.99, 95% CI 0.92 to 1.05; low certainty). Evidence for insulin degludec was very uncertain (RR 1.00, 95% CI 0.91 to 1.10; very low certainty). Insulin icodec may increase mild or moderate nocturnal hypoglycaemia (RR 1.23, 95% CI 1.01 to 1.51; low certainty).

For severe nocturnal hypoglycaemia, insulin detemir may result in a reduction compared with NPH insulin (RR 0.82, 95% CI 0.54 to 1.27; low certainty). Evidence for insulin glargine, insulin degludec and insulin icodec was very uncertain (RR 0.84, 95% CI 0.60 to 1.18 for insulin glargine; RR 1.09, 95% CI 0.53 to 2.27 for insulin degludec; RR 1.10, 95% CI 0.23 to 5.23 for insulin icodec; all very low certainty).

Events of DKA were uncommon. Compared with NPH insulin, insulin detemir may increase DKA (RR 1.46, 95% CI 0.24 to 9.08; low certainty), while evidence for insulin glargine, insulin degludec and insulin icodec was very uncertain, with relative risks of 0.75 (95% CI 0.17 to 3.37) for insulin glargine, 1.11 (95% CI 0.10 to 12.03) for insulin degludec and 3.36 (95% CI 0.06 to 180.89) for insulin icodec, with wide confidence intervals and very low certainty.

Evidence on quality of life and treatment adherence was limited and inconsistent. Effect estimates were small and imprecise (standardized mean difference ranging from -0.13 to 0.15 across long-acting insulin analogues compared with NPH insulin, with wide confidence intervals), and certainty of evidence was very low, largely due to open-label trial designs, inconsistency and reliance on patient-reported outcomes.

Data on mortality, macrovascular and microvascular complications, and accidents were sparse, with few events and very wide confidence intervals. No consistent differences between basal insulin analogues and NPH insulin were identified for these outcomes, and the certainty of evidence was very low.

Reported adverse events were generally infrequent and similar across intervention groups. Serious adverse events were uncommon, and no consistent safety signals were identified for any basal insulin type.

Overall, the certainty of the quantitative evidence ranged from moderate to very low. Major limitations included imprecision for rare events, heterogeneity in hypoglycaemia definitions and insulin titration protocols, short follow-up for long-term outcomes and risk of bias related to open-label designs and missing outcome data.

See Web Annex A Tables 5.1–5.6 for details of the evidence profiles.

Recommendation 4b

Characteristics of the evidence

Four RCTs contributed with data to the evidence profiles across three comparisons (dinner-time versus bedtime long-acting insulin; morning versus evening long-acting insulin; flexible versus fixed evening long-acting insulin). Most trials were conducted in outpatient specialist diabetes clinics. The enrolled population comprised adults of both sexes with a mean age ranging from 40 to 46 years, mean HbA1c from 7.6% to 8.1% and mean BMI from 24 to 27 kg/m^2. Trials were conducted in Europe and across multiple high-income countries. No trials were conducted in LMICs or in emergency or humanitarian settings, which substantially limits the applicability of findings to the range of health system contexts to which this guideline applies.

See Web Annex A for the summary of included studies.

Outcomes

Timing of basal insulin: dinner-time versus bedtime long-acting insulin

Two RCTs (Grimaldi 2007 and Hamann 2003) compared dinner-time with bedtime administration of insulin glargine, with follow-up of 6 to 6.5 months. Both were conducted in high-income European settings.

HbA1c was similar between groups (MD -0.03%, 95% CI -0.10 to 0.03; low certainty). All hypoglycaemia, severe hypoglycaemia and all nocturnal hypoglycaemia showed little to no difference, with confidence intervals crossing the line of no effect across all outcomes. DKA, mortality, microvascular and macrovascular complications, quality of life, body weight and adherence were not reported. Overall certainty ranged from low to very low, and no consistent outcome differences were identified between dinner-time and bedtime basal insulin administration.

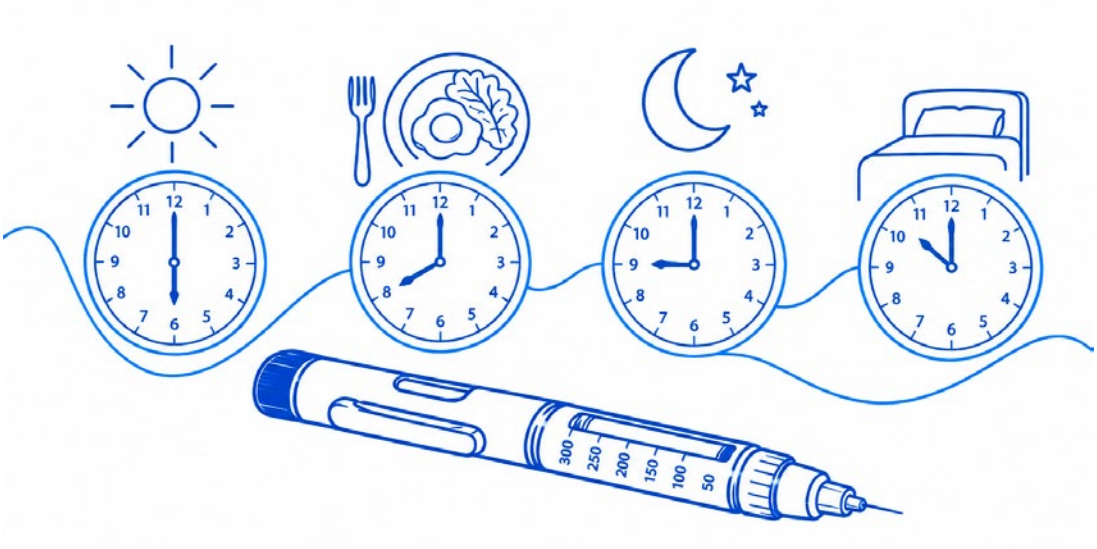
Timing of basal insulin: morning versus evening long-acting insulin

Two RCTs (EDITION 4 and Hamann 2003) compared morning with evening administration of long-acting insulin. EDITION 4 included insulin glargine 300 U/mL and glargine 100 U/mL as separate study arms; Hamann 2003 also included a breakfast versus bedtime comparison. Follow-up was 6 to 12 months.

HbA1c was equivalent between groups (MD -0.03%, 95% CI -0.16 to 0.10; moderate certainty), with both the point estimate and confidence interval well within the zone of no clinically important difference. Fasting blood glucose was modestly higher with morning administration in one trial (MD 1.3 mmol/L, 95% CI 0.59 to 2.01; low certainty). All hypoglycaemia showed no important difference (low certainty). For severe hypoglycaemia, morning dosing may have reduced risk (RR 0.54, 95% CI 0.29 to 1.03; very low certainty), but results were inconsistent across trials, and the confidence interval included no effect. Nocturnal hypoglycaemia showed no important difference (very low certainty). DKA, mortality, microvascular and macrovascular complications, quality of life, body weight, adherence and self-monitoring frequency were not reported. Overall certainty ranged from low to very low across most outcomes, with the exception of HbA1c (moderate certainty).

Timing of basal insulin: flexible versus fixed evening long-acting insulin

One RCT (BEGIN: Flex T1) compared flexible dosing of insulin degludec, administered at any time of day, with dosing intervals permitted to vary between 8 and 40 hours, with fixed once-daily evening dosing, over 26 weeks, across multiple high-income countries.



HbA1c was equivalent between groups (MD 0.00%, 95% CI -0.19 to 0.19; high certainty), providing conclusive evidence of no clinically important difference in glycaemic control. All incident hypoglycaemia was lower with flexible dosing (RR 0.94, 95% CI 0.91 to 0.98; moderate certainty), corresponding to approximately 60 fewer events per 1000. Severe hypoglycaemia, severe nocturnal hypoglycaemia and all nocturnal hypoglycaemia showed no differences, with wide confidence intervals (low certainty for each). DKA was very rare (one event in the fixed arm only; low certainty). Non-adherence to the trial insulin protocol was more likely with flexible dosing (RR 3.02, 95% CI 0.62 to 14.74), though the wide confidence interval precludes firm conclusions (low certainty). Body weight change showed no important difference between flexible and fixed evening dosing (MD 0.4 kg, 95% CI -0.26 to 1.06; high certainty). Retinopathy events were rare but more frequent with flexible dosing in a single trial (very low certainty); this finding is based on very few events and should be interpreted with caution. Macrovascular complications had zero events. Quality of life and self-monitoring frequency were not reported.

See Web Annex A Tables 3.3–3.5 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Economic evidence

Characteristics of the evidence

The economic evidence for offering intermediate and long-acting basal insulins to adults with type 1 diabetes was derived from published model-based economic evaluations, predominantly cost-utility analysis (CUA), comparing long-acting insulin analogues with NPH insulin or with other long-acting insulin analogues. The GDG was not presented with de novo health economic modelling.

A total of 22 economic evaluations directly informed comparisons relevant to intermediate and long-acting basal insulins. These included insulin glargine versus NPH insulin (7 studies), insulin detemir versus NPH insulin (12 studies), insulin degludec versus NPH insulin (1 study), insulin degludec versus insulin glargine (12 studies), insulin icodec versus insulin degludec (1 study) and insulin detemir versus insulin glargine (1 study).

Most studies were conducted in high-income countries, particularly in Europe and Canada, with a small number from upper-middle-income countries (Brazil, Colombia, Iran (Islamic Republic of), Serbia and Bulgaria). No economic evaluations were identified from low-income, humanitarian or emergency settings.

Nearly all studies were model-based, most commonly using the CORE Diabetes Model or similar cohort or decision-analytic frameworks. Time horizons ranged from 1 year to lifetime, with short-term models focusing on hypoglycaemia outcomes and longer-term models incorporating diabetes-related complications. Perspectives were most frequently health-care system or payer, with a small number adopting a societal perspective.

Across studies, industry funding dominated, particularly for evaluations of newer long-acting insulin analogues, with public or government funding reported in only a minority of analyses. Sensitivity analyses were commonly conducted, although the use and reporting of probabilistic sensitivity analysis varied.

Outcomes

The economic evidence suggests that long-acting insulin analogues may appear cost-effective compared with NPH insulin in modelling analyses. However, these findings rely heavily on assumptions regarding the price the manufacturer of the insulin is choosing to charge, reductions in hypoglycaemia and projected long-term complications, whereas RCTs showed no clinically important differences in HbA1c, hypoglycaemia or long-term outcomes across analogues, and no consistent reduction in hypoglycaemia, except for a lower hypoglycaemia risk with insulin detemir compared with NPH insulin. The results varied by insulin analogue type, modelling assumptions, including the price the manufacturer charges and setting.

For insulin glargine compared with NPH insulin, most studies reported cost-effectiveness or dominance. Reported incremental cost-utility ratios generally fell below country-specific WTP thresholds, with ICERs commonly ranging from US$ 7 362.89 to US$ 28 167.93 per QALY gained. Two studies reported insulin glargine dominating NPH insulin (more effective and less costly). However, one publicly funded study from a high-income setting reported a substantially higher ICUR of US$ 105 439.79 per QALY, indicating that cost-effectiveness was sensitive to assumptions regarding reductions in hypoglycaemia, the prices of the insulin and long-term modelling.

Compared with NPH insulin, most evaluations found insulin detemir to be cost-effective in at least one modelled scenario. Reported ICURs were typically below local WTP thresholds, with values ranging from US$ 888.37 to US$ 29 245 per QALY gained. One analysis found insulin detemir to be cost-effective when administered twice daily, but not when administered once daily. A small number of studies reported very high ICURs in long-term models, including values of US$ 464 928 per QALY and US$ 124 267 738 per QALY, reflecting uncertainty in extrapolated benefits.

In most studies comparing insulin degludec with insulin glargine, insulin degludec was found to be cost-effective or dominant, particularly in short-term models. Reported ICURs ranged from US$ 102 to US$ 32 719 per QALY gained, and six studies reported dominance. However, at least one long-term model reported a very high ICUR of US$ 82 117 134 per QALY, indicating that long-term cost-effectiveness was highly sensitive to modelling assumptions.

A single study comparing insulin icodec with insulin degludec found icodec to be the dominant option, with deterministic sensitivity analyses indicating robustness. Probabilistic sensitivity analysis suggested uncertainty in cost-effectiveness (probability approximately 40%), falling below the standard 50% threshold.

Across all comparisons, assumed reductions in hypoglycaemia, particularly severe or nocturnal hypoglycaemia, were the main drivers of incremental QALY gains and favourable cost-effectiveness estimates. Cost-effectiveness results were consistently sensitive to assumptions about hypoglycaemia rates, insulin acquisition costs, dosing regimens and the time horizon.

See Web Annex B Table 1 for details of the economic studies.

Rationale for judgement

Types of basal insulin

The GDG considered the choice of basal insulin for adults with type 1 diabetes to be a priority issue.

In 2018, WHO recommended the use of human insulin to manage blood glucose in adults with type 1 diabetes (strong recommendation, low-quality evidence), covering both short-acting (regular human insulin) and intermediate-acting (NPH insulin). A weak recommendation was also issued to consider long-acting insulin analogues for individuals with frequent severe hypoglycaemia, reflecting limited evidence of benefit for severe hypoglycaemia and substantially higher costs compared with human insulin. The GDG therefore re-examined the evidence to determine whether and how these recommendations should be updated.

The GDG judged that the desirable effects of long-acting insulin analogues compared with NPH insulin are small for most adults with type 1 diabetes. Randomized trials and meta-analyses showed little or no clinically important difference in HbA1c, and no consistent reduction in overall hypoglycaemia across all long-acting insulin analogues. Evidence suggesting a reduction in severe or nocturnal hypoglycaemia was observed only for insulin detemir, while evidence for other long-acting insulin analogues was inconsistent or insufficient. The GDG considered this potential benefit to be modest and uncertain at the population level, but possibly meaningful for individuals who experience recurrent severe hypoglycaemia.

The undesirable effects of both NPH insulin and long-acting insulin analogues were judged to be trivial or small. Serious adverse events were uncommon, and no consistent safety concerns were identified.

The overall certainty of the evidence was judged to be moderate. This reflects reasonably consistent findings of small effects across randomized trials, alongside important limitations, including short follow-up, imprecision for rare outcomes such as severe hypoglycaemia, heterogeneity in outcome definitions and limited evidence for long-term diabetes-related complications and mortality.

The GDG judged that values and preferences are likely to vary. Avoiding severe hypoglycaemia is highly valued, particularly among individuals with recurrent or nocturnal episodes. At the same time, many people with type 1 diabetes value affordability, treatment continuity and reliable access to insulin, which may favour NPH insulin in many settings. The GDG did not identify evidence of large variability in values overall, but recognized that preferences may differ depending on prior hypoglycaemia experience and local context. People using an insulin pen are likely to prefer glargine because glargine is most commonly given once a day and NPH twice. However, unlike glargine, NPH insulin can be mixed with short-acting insulin in one syringe, a combination typically used in the morning and reducing the number of injections.

The balance between benefits and harms was judged to favour NPH insulin as the preferred basal insulin option for most adults with type 1 diabetes, given its effectiveness, safety, wide availability and favourable and predictable resource-use profile. For adults with frequent severe hypoglycaemia (defined as two or more episodes of hypoglycaemia requiring the aid of another person per year), the GDG judged that the balance of benefits and harms may favour insulin detemir, particularly when hypoglycaemia persists despite appropriate use of NPH insulin and after addressing potentially preventable causes. The evidence

for other long-acting insulin analogues was insufficient to draw conclusions on severe hypoglycaemia, with very low certainty due to serious risk of bias and imprecision.

Resource requirements were judged to be large overall and highly variable by country and health system context, with particular importance in low-resource, emergency and humanitarian settings. Insulin price analyses presented to the GDG, based on retail prices from 89 countries between 2010 and 2025, indicate that although prices for both human insulin and long-acting insulin analogues have declined over time, long-acting insulin analogues remain consistently more expensive than human insulin. Over this period, median retail prices for long-acting insulin analogues declined by approximately 47% (from about US$ 6.76 to US$ 3.58 per 100 IU). However, switching from human to long-acting insulin analogues increases costs, with typical prices increasing from around US$ 2.00 per 100 IU for human insulin to US$ 3.58 per 100 IU for long-acting insulin analogues. The magnitude of this cost differential varies substantially across settings. In high-income countries, switching from NPH insulin to long-acting insulin analogues is typically associated with an increase of 50–60% in insulin acquisition costs, whereas in LMICs long-acting insulin analogues may cost approximately 2.6 to 2.8 times more than human insulin. In addition, total treatment costs may be further increased by the use of pen-based delivery systems, which in some lower-income markets may triple or quadruple overall insulin-related costs.

Economic evaluation findings rely heavily on model-based assumptions, most commonly, reductions in hypoglycaemia are frequently industry-funded and have limited generalizability to low-resource or humanitarian contexts. In contrast, NPH insulin was judged to have a more predictable, affordable and equitable resource-use profile across settings.

The impact on health equity was judged to vary. Preferential or widespread use of long-acting insulin analogues without clear clinical indications could exacerbate inequities in settings with constrained budgets or limited insulin supply. Maintaining NPH insulin as the preferred basal insulin option supports equitable access and continuity of care.

Both NPH insulin and long-acting insulin analogues were judged to be acceptable to people with type 1 diabetes and health-care providers. Feasibility was judged to be high for NPH insulin across all settings, and variable for long-acting insulin analogues depending on availability, affordability and supply-chain stability. Therefore, the GDG issued a conditional recommendation that either human insulin or insulin analogues can be used as basal insulin for adults with type 1 diabetes, with human insulin as the preferred option because it is in general less costly, reflecting small and uncertain benefits of insulin analogues at the population level and moderate overall certainty of evidence.

Timing of basal insulin

The GDG considered timing of long-acting insulin analogue administration for adults with type 1 diabetes to be a priority issue.

The GDG judged that the desirable effects of any specific injection timing were trivial or uncertain across all three comparisons examined (dinner-time versus bedtime, morning versus evening and flexible versus fixed evening administration). No clinically important differences in HbA1c were identified across comparisons. Evidence on hypoglycaemia and other outcomes was of low to very low certainty, and no consistent benefit signal was identified for any specific timing. The undesirable effects were similarly judged to be trivial or uncertain across most comparisons. The GDG noted one exception: a possible moderate increase in fasting blood glucose with morning administration compared with evening administration of insulin glargine, though certainty was low. The GDG also noted that flexible dosing of insulin degludec probably reduces incident hypoglycaemia compared with fixed evening dosing, with no difference in HbA1c, based on moderate-certainty evidence.

The overall certainty of the evidence was rated as low to very low, reflecting inconsistent certainty across comparisons and outcomes and the limited number of trials available for each comparison.

The GDG judged that there was possibly important to probably no important uncertainty or variability in how adults with type 1 diabetes value the critical outcomes.

The balance of benefits and harms was judged not to favour any specific timing over its comparator. Resource requirements were judged to involve negligible costs and savings, as the dose, device and monitoring requirements are identical regardless of injection timing, making timing-related decisions cost-neutral. No cost-effectiveness differences were anticipated. The impact on health equity was judged to be none, with the GDG noting that giving adults greater choice over injection timing may itself support equity by facilitating adherence across different daily circumstances. Acceptability was judged to be high, greater flexibility of regimen timing was considered highly acceptable to adults with type 1 diabetes. The GDG noted that training may be required for health-care providers who are accustomed to prescribing a specific timing. Feasibility was judged to be high.

Overall, the GDG made a conditional recommendation that once-daily long-acting insulin analogues can be given at the time of day preferred by the adult with type 1 diabetes, reflecting the absence of clinically important outcome differences across timing comparisons, negligible resource implications and high acceptability and feasibility. The GDG noted that the available evidence applies to insulin glargine and insulin degludec, and should not be generalized to NPH insulin.

Recommendations on bolus and basal insulins are shown in Fig. 2.

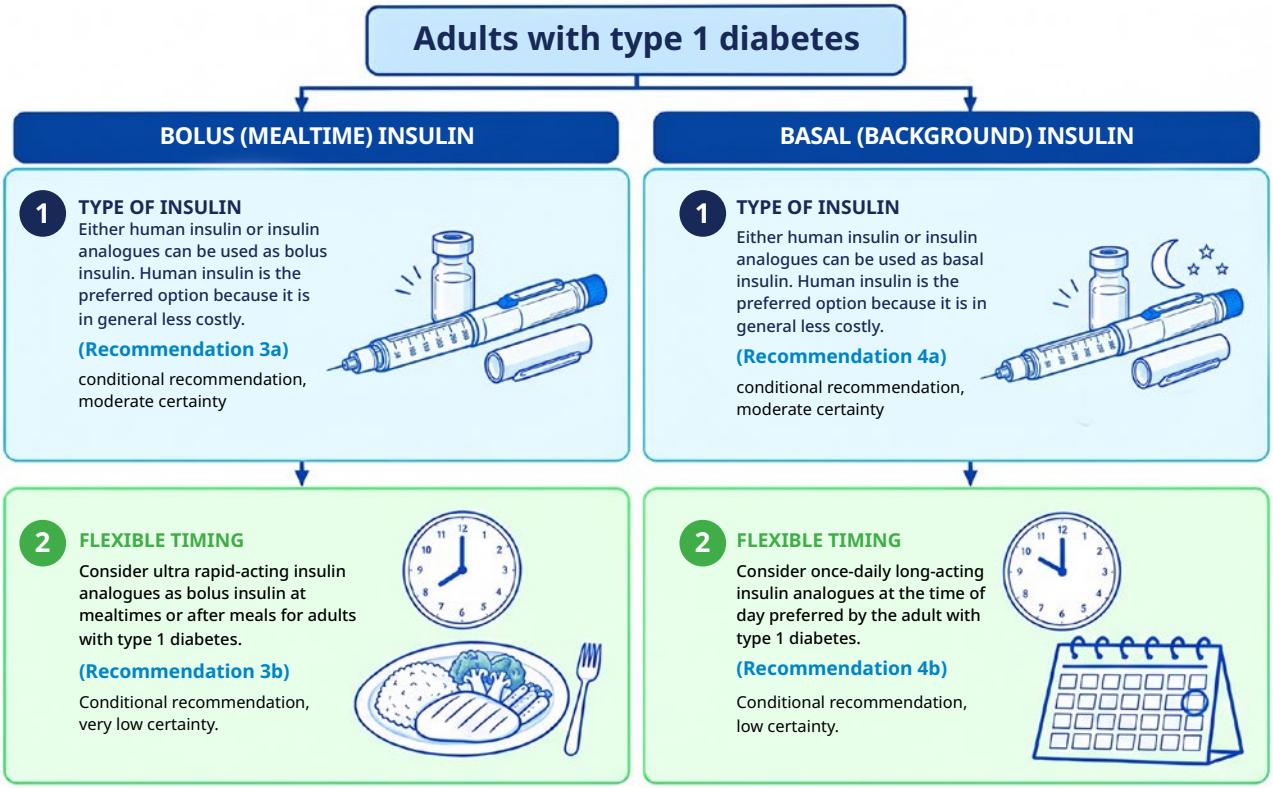


Fig. 2. Recommendations on bolus and basal insulins

3.2.4 Insulin mixing

Recommendation 5

- Consider premixed human insulin or self-mixed human insulin (NPH and regular human insulin drawn from separate vials or injected from separate pens) for adults with type 1 diabetes.
  (conditional recommendation, very low certainty)

Remarks

- The recommendation is relevant for people with type 1 diabetes who are not on the recommended intensified insulin treatment, whether by personal choice or by circumstances.

- The choice between premixed and self-mixed insulin should take into account local availability, relative cost and supply continuity, as these vary substantially across settings.

- Health-care providers should ensure that adults switching between premixed and self-mixed formats receive education on injection dose preparation and ad hoc dose adjustment to meal content and planned physical activity.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

One RCT contributed data to the evidence profile for this comparison. The trial was conducted in an outpatient setting in a low-income country and enrolled participants aged 11 to 28 years on a twice-daily insulin regimen. HbA1c data were available for only 12 participants in the intervention group and 11 participants in the comparison group. No trials were conducted in high-income countries or across multiple settings, which limits the generalizability of the findings. No trials comparing premixed and self-mixed insulin analogues were identified.

Outcomes

The RCT compared premixed human insulin (70% NPH/30% regular human insulin) with self-mixed insulin (NPH and regular human insulin combined by the patient) over 29 weeks. HbA1c showed no statistically significant difference between the groups (MD -0.8%, 95% CI -2.8 to 1.2), but the estimate was imprecise (very low certainty). The other outcomes were not reported.

See Web Annex A Table 3.6 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Rationale for judgement

The GDG considered the question of premixed versus self-mixed human insulin for adults with type 1 diabetes to be a priority issue because intensive treatment is sometimes not feasible.

The GDG judged that both the desirable and undesirable effects were uncertain. The available evidence consisted of a single small trial with data available only for HbA1c, and all other prespecified outcomes were not reported. The overall certainty of the evidence was rated as very low, reflecting serious imprecision, indirectness due to the young age of participants (11 to 28 years), which differs from the broader adult population addressed by this guideline, and the absence of data on hypoglycaemia, DKA, mortality or other critical outcomes.

The GDG judged that there was possibly important to probably no important uncertainty or variability in how adults with type 1 diabetes value the critical outcomes.

The balance of benefits and harms was judged to be uncertain. Resource requirements for premixed insulin were judged to involve moderate costs, as premixed insulin is generally more expensive than separate vials of NPH and regular human insulin, and the price difference may be a significant issue in some settings. No formal cost-effectiveness analysis was undertaken. The GDG noted that it is unlikely that the effectiveness of premixed insulin outweighs its additional costs in settings where premixed is

more expensive. However, cost considerations vary substantially by context, as in some settings premixed 70/30 insulin may be more accessible and affordable than sourcing two separate products. The GDG therefore judged cost-effectiveness to be context-dependent, varying and uncertain. Premixed insulin could reduce equity where it is less affordable than self-mixed insulin. It could also reduce equity by limiting the possibility of adjusting doses to blood glucose levels and changes in daily life, including food availability, composition and timing, exercise and intercurrent illness.

Conversely, where premixed insulin is more accessible or less expensive, it may support equity by simplifying access. Acceptability was judged to be high overall. Premixed insulin may be acceptable as it reduces the risk of dose preparation errors, though it may not be acceptable to some adults who have the possibility of self-monitoring, as it offers very little flexibility in daily life, including the ability to make ad hoc corrections for hyperglycaemia. Feasibility was judged to be high for both formats.

The GDG discussed whether a recommendation was warranted given the very limited evidence. However, the GDG concluded that a conditional recommendation was preferable to no guidance, as both formats are in clinical use across diverse settings and clinicians and patients benefit from a basis for decision-making in the absence of evidence of harm. The GDG emphasized that both premixed and self-mixed regimens are less flexible than intensified basal-bolus therapy and that intensified therapy should be used when accessible and feasible. Overall, the GDG made a conditional recommendation to consider either premixed or self-mixed human insulin for adults with type 1 diabetes, reflecting the insufficient evidence to favour one format over the other and the importance of using whatever insulin preparation is available.

3.2.5 Insulin delivery methods

Recommendation 6

Consider pens over syringes to deliver insulin in adults with type 1 diabetes.
(conditional recommendation, very low certainty)

Remarks

- Insulin pens may improve ease of use, dosing accuracy and convenience compared with syringes for some adults with type 1 diabetes, which may support adherence to insulin therapy.
- The choice between insulin pens and syringes should take into account availability, affordability, user preference and local health system capacity; lack of access to pens should not delay or prevent insulin treatment.
- In settings where pens are not available or feasible, insulin syringes remain an acceptable and effective option for insulin delivery.
- The use of pre-filled insulin pens may generate additional plastic waste; appropriate disposal practices should be encouraged to minimized environmental impact, where feasible.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

Six randomized crossover trials conducted between 1985 and 1994 were included, enrolling relatively small numbers of participants and undertaken predominantly in high-income European settings. One non-randomized study and one systematic review contributed additional contextual information, particularly for patient-reported outcomes.

Across trials, participants were adults with established type 1 diabetes receiving multiple daily insulin injections or premixed insulin regimens. Interventions involved early-generation insulin pen devices, while comparators were conventional vial and syringe delivery. Follow-up periods were ranging from 6 to 28 weeks, limiting the ability to assess longer-term clinical outcomes. Outcomes assessed included HbA1c, hypoglycaemia, adverse events, quality of life and patient preference.

Most randomized crossover trials had important methodological limitations. Randomization procedures and allocation concealment were often poorly described and sample sizes were small. Many outcomes, particularly patient preference and quality of life, were self-reported and therefore susceptible to response and expectation bias. Overall, risk of bias was judged to be serious to very serious across most outcomes.

See Web Annex A for the summary of included studies.

Outcomes

The available quantitative evidence showed no clinically important differences in glycaemic control between insulin pen devices and syringes. Across four randomized crossover trials reporting HbA1c outcomes (n = 111), mean HbA1c levels at follow-up were similar between delivery methods, with a pooled MD of 0.01% higher with pens (95% CI -0.22 to 0.24; very low certainty). Baseline HbA1c levels were variably reported, and the short duration of follow-up further limited interpretation of longer-term glycaemic effects.

Evidence on hypoglycaemia was limited and imprecise. Across randomized crossover trials, no meaningful differences in the frequency or rate of hypoglycaemic events were observed between pen and syringe use. Confidence intervals were wide, and several studies reported too few events to support robust statistical analysis, resulting in very low certainty.

Adverse events were generally minor and infrequently reported. Local injection-site reactions, such as haematoma or induration, occurred at similar frequencies across delivery methods, and no serious device-related safety concerns were identified. Some participants reported less pain with pen devices. However, these findings were based on self-reported outcomes and small samples. Certainty of evidence for adverse events was very low.

Patient-reported outcomes consistently favoured insulin pen devices. Across randomized crossover trials and non-randomized studies, a high proportion of participants reported pens to be easier to use, more convenient and preferable to continue using compared with syringes, and some reported improvements

in quality of life. Certainty of evidence for patient preference, ease of use and convenience was very low, as was certainty for quality of life, due to serious risk of bias, small sample sizes and short follow-up.

No randomized or observational evidence was identified for long-term diabetes-related complications, including microvascular or macrovascular complications, DKA, mortality, sustained adherence to insulin therapy, insulin wastage or environmental impact.

See Web Annex A Tables 6.1–6.8 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where patient preference was one of the studies' outcomes, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Economic evidence

Characteristics of the evidence

The economic evidence comparing insulin syringes and pens in adults with type 1 diabetes comprised two full economic evaluations and two conference abstracts. The two full economic evaluations assessed the cost-effectiveness of smart insulin pens compared with standard (non-connected) insulin pen devices and were conducted in high-income settings (Canada and Sweden). Both studies were model-based cost-effectiveness analyses adopting a societal perspective, using the IQVIA Core Diabetes Model, with time horizons ranging from 60 years to lifetime, and applying annual discount rates of 1.5–3%. Clinical inputs were primarily derived from single-arm trials and observational data, including assumptions regarding reductions in HbA1c and hypoglycaemia associated with smart pen use.

Two conference abstracts provided additional economic evidence. One abstract (Spain) evaluated smart insulin pens compared with standard pen-based care using a microsimulation model informed by DCCT data. The second abstract (Colombia) was the only identified economic evaluation directly comparing pen devices with syringe and vial use, employing a Markov model from a health system perspective over a five-year time horizon, with sensitivity analyses exploring discount rates and insulin price reductions. No full economic evaluations comparing pen devices with syringes were identified, and no studies were conducted in low-income, emergency or humanitarian settings.

See Web Annex B Tables 2 and 3 for details of the economic studies.

Outcomes

The available economic evidence suggested that pen-based insulin delivery, particularly smart pens, may be economically favourable compared with alternative delivery methods in some settings. However, the evidence was limited in scope, relied heavily on modelling assumptions and manufacturer-sponsored analyses, and provided very limited direct evidence comparing pen devices with syringes, particularly in low-resource, emergency or humanitarian contexts.

Across the economic evaluations and supporting abstracts, smart insulin pens were consistently reported to be cost-effective or cost-saving compared with standard pens. In the Canadian and Swedish

analyses, smart pens were dominant, with projected gains in quality-adjusted life years and reductions in long-term diabetes-related complications, based on modelling assumptions on glycaemic control and hypoglycaemia, which were not observed in the clinical evidence.

Economic evidence directly comparing pen devices with syringes was limited to a single conference abstract from Colombia. This analysis suggested that pen devices for NPH insulin administration were cost-effective compared with syringe and vial use. However, the evidence was reported only in abstract form, with limited methodological details, and therefore subject to substantial uncertainty.

Rationale for judgement

The GDG considered the choice of insulin delivery method to be a priority issue for adults with type 1 diabetes, given its relevance to daily self-management, treatment experience and long-term adherence to insulin therapy.

The GDG judged that the desirable effects of insulin pens compared with syringes are uncertain to modest. Available evidence does not demonstrate clinically important differences in glycaemic control or hypoglycaemia between delivery methods. However, across randomized crossover trials and non-randomized studies, insulin pens were consistently associated with greater ease of use, convenience, portability and user preference. These outcomes were considered important for supporting daily insulin administration and treatment satisfaction, even though they do not directly translate into improved clinical outcomes.

The undesirable effects of insulin pens were judged to be trivial. Reported adverse events were infrequent and minor, and no consistent safety concerns were identified. The GDG noted potential environmental considerations related to increased plastic waste from pre-filled pen devices, but considered these harms to be small and manageable through appropriate disposal practices.

The overall certainty of the evidence was judged to be very low. This reflects serious methodological limitations across studies, including small sample sizes, short follow-up, crossover designs with potential carryover effects, reliance on self-reported outcomes and imprecision. Evidence for critical and important outcomes was limited, and no trials directly evaluated long-term diabetes-related complications or mortality.

The GDG judged that values and preferences show little variability. Ease of use, convenience and confidence in insulin delivery were consistently valued by people with type 1 diabetes, although preferences may differ depending on individual circumstances and health system context.

Overall, the balance between benefits and harms was judged to be equal to probably favouring insulin pens, given consistent user preference and minimal harms, despite uncertainty in clinical effectiveness.

Resource requirements were judged to be moderate overall but highly variable by country and health system context. Evidence reviewed by the GDG indicates that acquisition and delivery costs for insulin pens are generally higher than for syringes and vials, with substantial variation by income setting. In high-

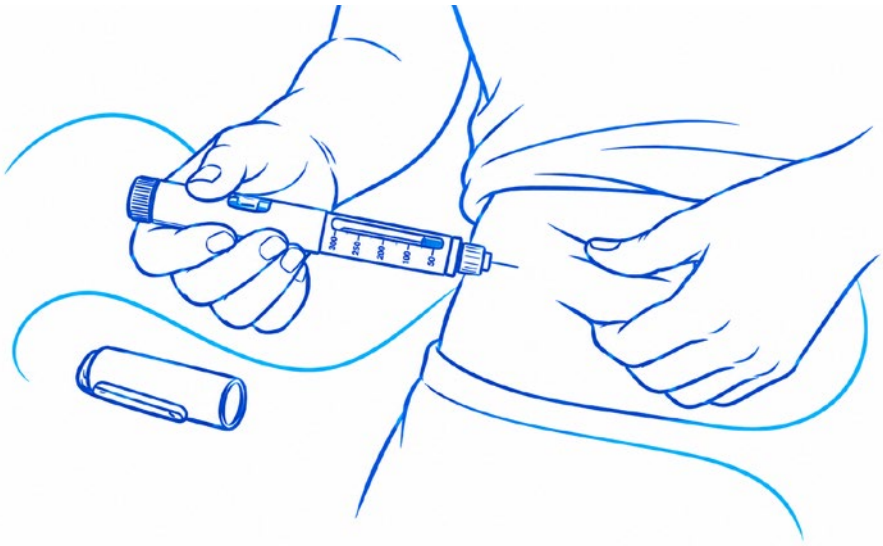
income countries, pen-based insulin delivery is common and benefits from large purchasing volumes, broader biosimilar availability and negotiated pricing, such that pens may appear similar in cost or, in some datasets, less expensive than vials. In contrast, in lower-income and lower-middle-income settings, insulin pens are often unaffordable and used only by a small proportion of people with diabetes. Price analyses presented to the GDG indicate that pen formulations may cost up to three times more than vials in these settings, and that switching from a vial-and-syringe regimen to a pen-based regimen, particularly for basal insulin, can triple or quadruple total insulin-related costs. These differences may be further amplified by the need for compatible cartridges, pen needles and more complex supply chains.

The GDG noted that economic evidence directly comparing insulin pens with syringes is limited and largely model-based, with substantial uncertainty and reliance on speculative assumptions about long-term adherence and reductions in complications. While insulin pens may be cost-effective in some high-income settings due to market dynamics, these findings are not readily generalizable to low-resource, emergency or humanitarian contexts. Overall, the GDG judged that insulin pens have a less predictable and more context-dependent resource-use profile than syringes, supporting a conditional rather than universal preference.

The impact on health equity was judged to potentially decrease or vary. Insulin pens may improve treatment experience where available, but limited access, affordability or supply constraints in lower-resource settings could exacerbate existing inequities if pens are preferentially recommended without ensuring sustainable access.

Insulin pens were judged to be acceptable to most people with type 1 diabetes and health-care providers. Feasibility was judged to be generally acceptable but context-dependent, requiring reliable access to devices, cartridges, needles and appropriate training.

Taking these considerations together, the GDG made a conditional recommendation in favour of insulin pens over syringes for adults with type 1 diabetes, reflecting very low certainty, modest but consistent benefits in usability and preference, minimal harms and important contextual considerations related to cost, equity and feasibility.



3.3 Clinical monitoring of glycaemic control

3.3.1 Frequency of monitoring

Recommendation 7

Offer HbA1c testing at up to three-monthly intervals to adults with type 1 diabetes.
(conditional recommendation, low certainty)

Remarks

- Use HbA1c testing to assess glycaemic control and inform clinical management.
- Apply the recommended frequency flexibly, recognizing that some individuals may require more or less frequent testing depending on clinical circumstances and stability of glycaemic control. More frequent testing may be considered if treatment has been changed recently or there is an unexpected rise in HbA1c.
- Availability, affordability and access to HbA1c testing may be limited in some settings; lack of access should not delay or prevent clinical care.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

The evidence informing this recommendation was derived from one RCT and two observational studies.

The RCT by Larsen et al. (1990) in adults with type 1 diabetes had HbA1c measured approximately every three months in both study groups. In the intervention group, results were provided to clinicians at every visit to guide treatment adjustments, while in the control group, results were measured but not entered into patient records and not communicated to providers.

The two observational studies examined HbA1c testing frequency in routine clinical care. These included the Diabetes Patienten Verlaufsdokumentation (DPV) registry study and the SEARCH for Diabetes in Youth Study (SEARCH). Both studies compared approximately three-monthly HbA1c testing with less frequent testing patterns (six-monthly or less frequent, depending on the study).

Across studies, there was heterogeneity in study design, exposure definitions and outcome measures. As a result, findings were narratively synthesized.

See Web Annex A for the summary of included studies.

Outcomes

The available quantitative evidence primarily reported glycaemic control outcomes, measured as mean HbA1c levels or categorical definitions of glycaemic control. Evidence on clinical complications was limited.

In the DPV registry study, mean HbA1c varied across categories of testing frequency. Individuals receiving 7–9 HbA1c tests over two years had a lower mean HbA1c compared with those tested less frequently, while those with very frequent testing (more than 9 tests over two years) had a higher mean HbA1c. These findings should be interpreted cautiously as they do not establish a causal association between testing frequency and HbA1c and likely reflect underlying differences in clinical characteristics.

In the SEARCH study, individuals receiving three or more HbA1c tests per year had a lower mean HbA1c compared with those tested less frequently. After adjustment for measured confounders, more frequent testing was associated with a lower mean HbA1c (MD -0.33%, 95% CI -0.50 to -0.16; very low certainty). Although there was a reduction in HbA1c, it likely reflected differences in clinical characteristics or intensity of follow-up rather than a direct effect of testing frequency.

In the RCT, more frequent reporting of HbA1c results to clinicians was not associated with a higher likelihood of achieving good glycaemic control (RR 0.93, 95% CI 0.65 to 1.34; low certainty) or a lower likelihood of poor glycaemic control (RR 2.27, 95% CI 1.04 to 4.98; very low certainty). These findings should be interpreted cautiously given serious risk of bias and imprecision.

Evidence for microvascular complications was limited to one observational study. In the SEARCH study, more frequent HbA1c testing was associated with lower odds of any microvascular complication in fully adjusted analyses (adjusted odds ratio 0.70, 95% CI 0.46 to 1.07; low certainty), although the confidence interval includes the possibility of no important effect.

No evidence was identified that directly evaluated the effect of HbA1c testing frequency on mortality, DKA, quality of life or access to therapies or technologies in people with type 1 diabetes.

Overall, the certainty of the evidence ranged from low to very low, primarily due to indirectness in the randomized trial, residual confounding in observational studies, inconsistency in exposure definitions and outcome reporting and very serious imprecision for several outcomes.

See Web Annex A Table 7.1 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Rationale for judgement

The GDG agreed that the frequency of HbA1c monitoring is important because it informs treatment adjustments over time.

The GDG judged that the desirable effects of offering HbA1c testing at up to three-monthly intervals are small to moderate and uncertain. Available evidence suggests positive associations between more frequent testing and improved glycaemic outcomes, but the GDG noted that the independent effect of testing frequency is difficult to disentangle from other aspects of more intensive follow-up and care. The undesirable effects were judged to be trivial and uncertain, as HbA1c testing is generally safe, with potential downsides mainly related to access, inconvenience and downstream costs rather than direct harm.

The overall certainty of the evidence was rated as low, reflecting limitations in study design, residual confounding in observational studies and indirectness of evidence from trials where testing frequency could not be isolated from broader care packages.

The GDG judged that how people value the critical outcomes probably varies and/or is uncertain, recognizing differences in individual preferences, access to testing and health system contexts. While maintaining good glycaemic control is universally important, the acceptability and perceived value of frequent testing may differ depending on feasibility and burden.

Overall, the GDG concluded that the balance between benefits and harms probably favours increased frequency of HbA1c testing, while acknowledging uncertainty in the benefit.

Resource requirements were judged to be moderate and variable, depending on availability of HbA1c testing, laboratory capacity and financing arrangements across settings. No direct evidence was available to inform the certainty of resource use. The GDG judged that increased testing frequency would probably favour cost-effectiveness, given its potential to support improved glycaemic management and reduce complications over time.

The impact on health equity was judged to vary, as increased testing frequency could improve care where HbA1c testing is accessible, but may exacerbate inequities in settings with limited availability or affordability. The GDG judged increased testing frequency would be probably acceptable to people with type 1 diabetes and health-care providers. Feasibility was judged to vary and likely remains uncertain, particularly in low-resource and humanitarian settings.

For these reasons, the GDG made a conditional recommendation in favour of offering HbA1c testing at up to three-monthly intervals, reflecting low certainty, probable benefit over minimal harm and important variation in resources, feasibility and equity across settings.

3.3.2 Glycaemic targets

Recommendation 8

Aim to achieve an HbA1c of ≤ 7.0% (53 mmol/mol) in most adults with type 1 diabetes.
(conditional recommendation, moderate certainty)

Remarks

- The HbA1c target of ≤ 7.0% (53 mmol/mol) should be applied to most adults with type 1 diabetes as a general goal for glycaemic management.
- The target of ≤ 7.0% (53 mmol/mol) can rarely be achieved with one or two daily injections of insulin. Increasing the insulin dosage in people whose glycaemia remains above the recommended target range and who are on non-intensive regimens will be limited by an increased risk of hypoglycaemia.
- Individualized HbA1c targets may be appropriate, taking into account factors such as risk of hypoglycaemia, duration of diabetes, comorbidities, life expectancy and individual preferences.
- Achieving and maintaining HbA1c targets depends on access to insulin, glucose monitoring, diet, physical activity, diabetes education and ongoing clinical support; limitations in access should be considered when applying this recommendation.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

The evidence informing this recommendation was derived entirely from the DCCT and its long-term observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Sixteen reports were included, all originating from a single randomized trial (DCCT) and its long-term observational follow-up (EDIC). The DCCT was a multicentre RCT conducted across 21 centres in North America and enrolled adolescents and adults aged 13–39 years, with adult-relevant evidence derived from subgroup analyses and long-term follow-up. Participants were randomly assigned to intensive or conventional diabetes therapy within two prespecified cohorts: a primary-prevention cohort (diabetes duration 1–5 years, no retinopathy, normoalbuminuria) and a secondary-prevention cohort (diabetes duration 1–15 years, minimal retinopathy, albuminuria ≤200 mg/24 h).

Intensive therapy aimed to achieve near-normoglycaemia through multiple daily insulin injections or continuous subcutaneous insulin infusion, frequent self-monitoring of blood glucose (SMBG) and regular clinical follow-up, while conventional therapy reflected standard care at the time without a specific HbA1c target. HbA1c was measured centrally, and major microvascular outcomes, including retinopathy, nephropathy and neuropathy, were assessed using standardized, centrally adjudicated methods.

Following a mean randomized follow-up of approximately 6.5 years, participants entered the EDIC observational phase, during which outcomes were assessed at regular intervals under routine clinical care, allowing evaluation of long-term effects associated with prior glycaemic exposure.

Outcomes

The available quantitative evidence primarily reported microvascular outcomes, including diabetic retinopathy, nephropathy and neuropathy, as well as selected macrovascular outcomes during long-term follow-up. Glycaemic exposure was assessed through achieved mean HbA1c levels rather than through direct comparisons of prespecified HbA1c targets. The comparison reflects intensive glycaemic control targeting HbA1c <6.05% versus conventional therapy without a defined target (historically up to approximately 13.5%).

During the randomized phase of the DCCT (mean follow-up approximately 6.5 years; n = 1441), intensive glycaemic management, which achieved a mean HbA1c of ~7% compared with ~9% in the conventional treatment group, was associated with substantial reductions in microvascular complications. Intensive therapy reduced the risk of development or progression of retinopathy, nephropathy (including microalbuminuria and albuminuria) and clinical neuropathy, with consistent effects across both primary-prevention and secondary-prevention cohorts.

Long-term follow-up in the EDIC study demonstrated persistent benefits of earlier intensive glycaemic control despite subsequent convergence of HbA1c levels between the original treatment groups. Over extended follow-up (up to 18–24 years in different analyses), prior intensive therapy was associated with sustained reductions in microvascular complications and lower rates of major cardiovascular events in long-term follow-up, although evidence for macrovascular outcomes remains limited.

No randomized trials directly compared an HbA1c target of ≤7.0% (53 mmol/mol) with higher HbA1c targets. The evidence therefore reflects associations between achieved HbA1c levels and clinical outcomes rather than target-driven comparisons. Severe hypoglycaemia was increased with intensive therapy during the randomized treatment phase, but this did not negate the overall benefit observed for microvascular outcomes. DKA and all-cause mortality were also reported, but evidence was limited and of low to very low certainty due to few events and wide confidence intervals.

Overall, the certainty of the evidence was rated as moderate. Although the evidence is derived from a single randomized trial and its long-term observational extension, the magnitude and consistency of effects across clinically important outcomes, long duration of follow-up and robust outcome adjudication support moderate confidence in the estimated effects, despite reliance on a single trial and indirectness arising from comparisons of achieved HbA1c rather than prespecified targets.

See Web Annex A Table 8.1 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Rationale for judgement

The GDG considered aiming for specific HbA1c targets to be an important component of glycaemic control in reducing the risk of long-term diabetes-related complications.

The GDG judged that aiming for a lower HbA1c target is associated with large benefits for microvascular outcomes, with some outcomes judged to have moderate benefit. Evidence from randomized and long-term follow-up studies demonstrates that lower achieved HbA1c levels are associated with substantial reductions in retinopathy, nephropathy and neuropathy. These benefits were observed across different subgroups and persisted during extended follow-up.

The GDG also judged that the harms associated with lower HbA1c targets are moderate overall, with some outcomes potentially large. In particular, more intensive glycaemic control was associated with higher rates of severe hypoglycaemia. The GDG noted that the balance between benefits and harms may differ for some populations, including older adults, people with comorbidities and individuals in emergency or humanitarian settings, but did not find sufficient evidence for justifying specific HbA1c values for a higher target.

The overall certainty of the evidence was judged to be moderate. High certainty evidence supports reductions in retinopathy progression and increased severe hypoglycaemia with intensive glycaemic control, while several other critical outcomes were supported by moderate or lower certainty evidence. This judgement reflects reliance on a single large RCT and its long-term follow-up with variation in certainty across outcomes.

The GDG judged that how people value the critical outcomes shows major variability and uncertainty. While prevention of long-term diabetes-related complications is highly valued, individuals may differ in their tolerance of hypoglycaemia risk, treatment burden and feasibility of achieving lower HbA1c targets, depending on personal circumstances and health system context.

Overall, the GDG concluded that the balance between benefits and harms favours a lower HbA1c target for most adults with type 1 diabetes, primarily due to substantial reductions in microvascular complications despite an increased risk of severe hypoglycaemia, while recognizing that this balance may differ across settings or populations.

Resource requirements were judged to be moderate, reflecting the need for access to insulin, glucose monitoring, clinical follow-up and education to safely achieve lower HbA1c levels. No direct evidence was identified on the certainty of resource use. The GDG judged that aiming for a lower HbA1c target would probably be cost-effective, given the prevention of costly long-term diabetes-related complications.

The impact on health equity was judged to potentially decrease or vary, as achieving lower HbA1c targets may be more difficult in settings with limited access to insulin, monitoring technologies or specialist care. Acceptability and feasibility were also judged to vary across settings and individuals.

The GDG therefore made a conditional recommendation in favour of aiming for an HbA1c of ≤7.0% (53 mmol/mol) in most adults with type 1 diabetes, while emphasizing the need for individualization based on clinical circumstances, patient preferences and resource availability.

3.4 Self-monitoring of glycaemia

3.4.1 Methods

Recommendation 9

- Consider self-monitoring by fingerstick testing, real-time continuous glucose monitoring (rtCGM) or intermittently scanned (flash) continuous glucose monitoring (isCGM) in adults with type 1 diabetes.

(conditional recommendation, moderate certainty)

Remarks

- Blood glucose monitoring is used to support safe adjustment of insulin dosage, and insulin dose adjustment should be done according to an agreed plan with a health professional. The plan should specify when self-adjustment is appropriate and when clinical review is needed.

- When rtCGM or isCGM (flash) is used, access to fingerstick blood glucose testing may still be required for calibration and to confirm readings when glucose values do not match symptoms or when readings are suspected to be inaccurate, including during the initial period after starting a new sensor.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

Evidence consisted of 17 RCTs evaluating self-monitoring methods in adults with type 1 diabetes. These trials compared real-time continuous glucose monitoring (rtCGM), intermittently scanned continuous glucose monitoring (isCGM) with conventional fingerstick SMBG, as well as limited head-to-head comparisons between continuous glucose monitoring (CGM) modalities.

Most trials were multicentre studies conducted in outpatient specialist diabetes clinics and enrolled adults with established type 1 diabetes receiving intensive insulin therapy, including multiple daily injections and, in some trials, continuous subcutaneous insulin infusion. The majority of studies were conducted in high-income settings, with limited representation from lower- and middle-income countries. Sample sizes ranged from small trials enrolling fewer than 100 participants to large multicentre trials enrolling more than 700 participants. Follow-up durations were typically 24 to 26 weeks, with a small number of trials extending to 12 months or longer, limiting assessment of long-term clinical outcomes.

Across studies, there was heterogeneity in baseline glycaemic control, frequency of fingerstick testing, outcome definitions (particularly for hypoglycaemia and patient-reported outcomes). Most trials were open-label, reflecting the nature of the interventions, contributing to risk of bias for some outcomes.

See Web Annex A for the summary of included studies.

Outcomes

Across randomized trials, rtCGM was associated with a small reduction in HbA1c compared with fingerstick SMBG (MD -0.28%, 95% CI -0.45 to -0.11; high certainty), while isCGM showed little to no difference (MD -0.22%, 95% CI -0.46 to 0.01; high certainty). However, both estimates were small and below the prespecified MCID of 0.5%. A trial by Visser et al. (2021) showed little to no difference in HbA1c between rtCGM and isCGM (moderate certainty).

RtCGM was associated with lower glucose variability compared to isCGM (moderate certainty) and fingerstick SMBG (high certainty).

Evidence on hypoglycaemia varied by outcome definition and monitoring modality. For severe hypoglycaemia incidence, in rtCGM versus fingerstick monitoring, low-certainty evidence suggested a possible increase in incidence but the result is also compatible with no difference, whereas the percentage of time spent in severe hypoglycaemia was reduced with moderate certainty. Evidence from one head-to-head trial suggested fewer severe hypoglycaemia events with rtCGM than isCGM, but this finding was based on a single study. For non-severe hypoglycaemia and time spent below target range, several trials reported reductions with CGM compared with SMBG, although heterogeneity in outcome definitions and reporting limited certainty, which ranged from low to moderate.

isCGM was associated with a statistically significant increase in time in target glucose range (MD 6.44 percentage points, 95% CI 4.43 to 8.45; moderate certainty). For rtCGM, the estimated increase was imprecise with a wide confidence interval that included possible harm (MD 5.65 percentage points, 95% CI -2.54 to 13.84; moderate certainty).

DKA was uncommon across trials, and the available evidence did not demonstrate consistent differences between monitoring methods. Certainty of evidence for this outcome was low to very low, due to few events and imprecision.

Several trials reported patient-reported outcomes such as treatment satisfaction or perceived burden, but measures were heterogeneous and certainty was low to very low.

Adverse events related to monitoring methods were generally rare. For CGM, reported events included mild skin irritation or sensor-related issues, and no consistent serious safety concerns were identified. Certainty of evidence for adverse events was low.

Overall, the certainty of the quantitative evidence ranged from moderate to low, depending on the outcome. Certainty was highest for HbA1c and time in range outcomes and lowest for rare clinical outcomes such as severe hypoglycaemia and DKA, reflecting short follow-up, imprecision for rare events, heterogeneity in outcome definitions and limitations related to open-label trial designs.

See Web Annex A Tables 9.1–9.3 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Economic evidence

Characteristics of the evidence

The economic evidence comparing self-monitoring methods in adults with type 1 diabetes comprised 19 economic evaluations, including CUA and CEA. These evaluations assessed rtCGM and isCGM against SMBG, as well as a smaller number of comparisons between rtCGM and isCGM.

For rtCGM versus SMBG, 12 evaluations were identified. These were conducted predominantly in high-income settings (Canada, France, Spain, United Kingdom of Great Britain and Northern Ireland, United States of America), with one evaluation from an upper-middle-income setting (Iran (Islamic Republic of)) and additional multi-comparator analysis from Denmark and Australia. For isCGM versus SMBG, seven evaluations were identified, conducted in high-income settings (Canada, Finland, Sweden, United Kingdom of Great Britain and Northern Ireland) and upper-middle-income settings (Brazil, China). For rtCGM versus isCGM, three evaluations were identified (Australia, Belgium and Denmark). In addition, three studies evaluated multiple comparators (rtCGM, isCGM and SMBG) and were split for presentation of findings by comparison.

All included economic evaluations were model-based, most commonly using established diabetes simulation frameworks (e.g. IQVIA Core Diabetes Model, Sheffield type 1 diabetes models, Markov cohort simulations and microsimulation approaches). Time horizons ranged from one year to lifetime, with most analyses using long-term horizons to capture downstream differences in diabetes-related complications. Perspectives varied and included public payer, health-care payer, societal and private payer perspectives. Most studies applied discounting to costs and outcomes and all reported sensitivity analyses, although the conduct and reporting of probabilistic sensitivity analyses varied across studies.

A substantial proportion of evaluations were funded by CGM manufacturers, particularly for rtCGM and for rtCGM versus isCGM comparisons. No economic evaluations were identified from low-income settings, nor from emergency or humanitarian contexts. Across studies, assumed effects on HbA1c, hypoglycaemia, DKA and quality of life constructs (including fear of hypoglycaemia and burden of monitoring) were the main drivers of modelled benefits.



Outcomes

Across economic evaluations, rtCGM was generally found to be cost-effective compared with conventional SMBG, although reported ICERs varied substantially by setting, model structure and key assumptions. Reported ICERs most commonly ranged from approximately US$ 7 805 to US$ 4 860 450 per quality-adjusted life year gained, remaining below country-specific WTP thresholds in most analyses. A minority of studies reported substantially higher ICERs or cost-effectiveness that was highly sensitive to assumptions, particularly device acquisition costs and the magnitude of assumed utility gains. In sensitivity analyses, cost-effectiveness for rtCGM was most sensitive to assumptions regarding quality of life benefits (including fear of hypoglycaemia and burden of monitoring), glycaemic effects and CGM price. In several models, rtCGM became dominant (more effective and less costly) when device prices were reduced or when disutility associated with hypoglycaemia was increased.

For isCGM compared with SMBG, all identified economic evaluations reported cost-effective results, and at least one evaluation reported superiority, with improved health outcomes at lower overall costs. Reported ICERs ranged from US$ 7 448 to US$ 43 398 per QALY gained, reflecting lower device costs and modest gains in quality-adjusted life years. Findings were commonly robust in deterministic and probabilistic sensitivity analyses, although cost-effectiveness estimates were sensitive to assumptions about acute event rates, particularly DKA, which was a key driver of projected cost savings in several models.

For rtCGM compared with isCGM, economic evaluations generally reported rtCGM to be cost-effective, and one evaluation reported dominance. Results for this comparison were driven primarily by assumed incremental reductions in HbA1c and hypoglycaemia outcomes, as well as by the relative prices of the two technologies. Reported ICERs varied widely, reflecting uncertainty in incremental benefit estimates. All economic evaluations identified for this comparison were manufacturer funded, and their applicability to settings with constrained resources was therefore judged to be uncertain.

Overall, the economic evidence suggests that both rtCGM and isCGM may represent good value for money compared with SMBG in adults with type 1 diabetes in several high-income and some upper-middle-income settings. Device price, assumptions regarding quality of life benefits and reductions in acute events were the principal drivers of cost-effectiveness. However, confidence in generalizability is limited by the predominance of model-based analyses, restricted geographic representation, frequent manufacturer funding and the absence of evaluations from low-income, emergency or humanitarian settings, where feasibility, affordability and continuity of supply may differ substantially.

See Web Annex B Table 4 for details of the economic studies.

Rationale for judgement

The GDG considered self-monitoring central to managing insulin safely.

In 2013, WHO recommended self-monitoring and self-adjusting insulin dosages for people with type 1 diabetes according to an agreed action plan with a health professional, as part of the WHO PEN, based on very low certainty. WHO also recommended that people with diabetes using insulin should be offered SMBG based on individual clinical need. The current guideline revisits and updates these recommendations in light of new randomized, economic and implementation evidence, and explicitly considers newer monitoring modalities, such as rtCGM and isCGM.

The GDG judged that the desirable effects of blood glucose self-monitoring using rtCGM or isCGM are overall moderate to large compared to fingerstick testing. Randomized trials demonstrated small but consistent improvements in glycaemic outcomes, including reductions in HbA1c and increases in time spent in target glucose range, for both rtCGM and isCGM compared with fingerstick testing. Evidence suggested a small additional benefit of rtCGM compared with isCGM in one randomized trial, although the certainty of this comparison was lower due to reliance on a single study. These benefits were considered meaningful for supporting day-to-day insulin adjustment and reducing glycaemic variability, even where effects on rare clinical outcomes were uncertain.

The GDG judged the undesirable effects of blood glucose self-monitoring to be trivial. Reported adverse events related to CGM use were infrequent and generally mild, including local skin irritation or sensor-related issues. No consistent serious safety concerns were identified across monitoring modalities.

The overall certainty of the evidence was judged to be moderate. Certainty was highest for HbA1c and time in range outcomes and lower for rare clinical outcomes such as severe hypoglycaemia and DKA, reflecting short follow-up, low event rates, heterogeneity in outcome definitions and open-label trial designs. Despite these limitations, the direction of effect across studies was consistent.

The GDG judged that values and preferences show minor variability. People with type 1 diabetes consistently value timely, actionable glucose information to support insulin adjustment and reduce uncertainty in daily management. Preferences for specific monitoring modalities may vary depending on lifestyle, comfort with technology and access, but no major variability in how critical outcomes are valued was identified.

Overall, the balance between benefits and harms was judged to favour blood glucose self-monitoring using rtCGM or isCGM. For comparisons between CGM modalities, the balance was judged to probably favour rtCGM over isCGM, although uncertainty remains due to limited direct comparative evidence.

Resource requirements were judged to be large and highly variable by setting. Fingerstick monitoring requires ongoing access to test strips, lancets and meters, while CGM systems involve higher acquisition and recurrent costs related to sensors, transmitters and readers. Economic evaluations conducted primarily in high-income and some upper-middle-income settings suggest that both rtCGM and isCGM may be cost-effective compared with fingerstick monitoring when assessed against country-specific WTP thresholds, with results sensitive to device prices, assumptions about quality of life benefits and reductions in acute events. The GDG noted substantial uncertainty regarding affordability and sustainability in low-resource, emergency and humanitarian settings.

The impact on health equity was judged to potentially decrease or vary. Expanded use of CGM technologies may improve care where available, but limited access, affordability and supply constraints could exacerbate inequities if such technologies are preferentially recommended without ensuring sustainable provision. Maintaining fingerstick testing as an acceptable option was considered important for equity and continuity of care.

The GDG judged blood glucose self-monitoring to be acceptable to adults with type 1 diabetes and health-care providers. Feasibility was judged to be generally acceptable but context-dependent, requiring reliable

access to supplies, appropriate training and integration into clinical care. Adjustment of insulin dosage should be undertaken according to an agreed plan with a health professional.

Overall, the GDG made a conditional recommendation in favour of SMBG using fingerstick testing, rtCGM or isCGM for adults with type 1 diabetes, reflecting moderate certainty, small but consistent benefits, minimal harms and important considerations related to cost, equity and feasibility across settings. Importantly, fingerstick testing was retained as an acceptable option.

3.4.2 Frequency

Recommendation 10

- Consider frequent self-monitoring of blood glucose in adults with type 1 diabetes, three or more times per day.
  (conditional recommendation, very low certainty)

Remarks

- The recommended frequency reflects a minimum intensity of monitoring to support safe insulin use and day-to-day glycaemic management in adults with type 1 diabetes.
- When rtCGM or isCGM is used, continuous or near-continuous glucose data inherently exceeds this minimum frequency.
- Individualize the appropriate frequency of monitoring, taking into account insulin regimen, risk of hypoglycaemia, daily activities, intercurrent illness and access to monitoring technologies and supplies.
- Consider urine glucose testing as an alternative only when blood glucose testing is not available.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

The evidence informing this recommendation was derived from three studies evaluating the frequency of SMBG in adults with type 1 diabetes *(29)*. These included one RCT and two observational studies. No eligible studies were identified that evaluated the timing of self-monitoring or specific glycaemic target values for SMBG.

The RCT by Skeie et al. (2009) was conducted in Norway and compared a structured SMBG approach (using a 10-point profile over three days) with routine self-monitoring over a nine-month follow-up period. The two observational studies were conducted in Germany/Austria and the United States of America, with follow-up periods ranging from 12 to 24 months, and examined associations between SMBG frequency and glycaemic outcomes in routine care settings.

Across studies, the primary outcome reported was glycaemic control measured by HbA1c. No studies reported outcomes related to hypoglycaemia, DKA, long-term diabetes-related complications, mortality or patient-reported outcomes.

See Web Annex A for the summary of included studies.

Outcomes

In the single RCT, a higher frequency of SMBG using a structured 10-point blood glucose profile may reduce HbA1c compared with once-daily SMBG. At nine months, HbA1c was 0.66% lower in the intervention group than in the control group (MD -0.66%, 95% CI -0.94 to -0.38).

The certainty of evidence for this outcome was rated as very low due to concerns about risk of bias, indirectness of the intervention and imprecision related to the small sample size. The two observational studies provided supportive but very low-certainty evidence that more frequent SMBG is associated with better glycaemic control. In one large registry study, mean HbA1c decreased progressively with increasing SMBG frequency, from approximately 8.3% among individuals testing one to three times per day to approximately 7.7% among those testing more than six times per day. In the second study, HbA1c was lower (MD -1.0%, 95% CI -1.3 to -0.8) among individuals who monitored SMBG at least three times per day compared with those who monitored less frequently.

Although all studies showed a consistent direction of effect favouring more frequent SMBG, the observational designs, residual confounding and heterogeneity in exposure definitions substantially limit confidence in these findings. The certainty of evidence for HbA1c from observational studies was therefore rated as very low.

No evidence was identified for other critical or important outcomes, including hypoglycaemia, DKA, long-term diabetes-related complications, mortality or patient-reported outcomes.

Overall, the certainty of the quantitative evidence supporting more frequent SMBG was judged to be very low.

See Web Annex A Table 10.1 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Rationale for judgement

The GDG considered monitoring frequency essential for safe insulin use.

The GDG judged that the desirable effects of more frequent self-monitoring are likely to be moderate. Evidence from one RCT and two observational studies consistently showed that higher frequencies of SMBG were associated with lower HbA1c levels but the frequency of SMBG was different across studies.

Although the certainty of this evidence was very low, the direction of effect was consistent across study designs and settings, and the observed differences in HbA1c were considered clinically relevant for many adults with type 1 diabetes. The GDG noted that even modest improvements in glycaemic control may contribute meaningfully to long-term risk reduction when sustained over time.

The undesirable effects of more frequent self-monitoring were judged to be uncertain to trivial. Potential harms discussed included discomfort related to fingerstick testing, burden of monitoring and the possibility of increased anxiety or distress associated with frequent measurements. However, no studies directly evaluated these outcomes, and no evidence of serious harm was identified. The GDG considered that these potential downsides would vary substantially between individuals and contexts and could be mitigated through appropriate education, shared decision-making and the use of alternative monitoring technologies where available.

The GDG judged the overall certainty of the evidence to be very low. This judgement reflects reliance on a single RCT with methodological limitations and indirectness, as the trial evaluated a structured 10-point blood glucose profile rather than a simple frequency threshold of three or more tests per day, as well as observational studies in which people who tested more frequently may have differed from those who tested less frequently in ways that independently improve glycaemic outcomes. In addition, evidence was limited to HbA1c outcomes, with no data available for other critical outcomes such as hypoglycaemia, DKA, long-term diabetes-related complications, mortality or patient-reported outcomes.

The GDG judged that values and preferences show possibly important variability. Adults with type 1 diabetes generally value access to glucose information to support insulin adjustment and self-management, but preferences regarding the intensity and frequency of monitoring are likely to differ based on lifestyle, risk of hypoglycaemia, access to supplies and comfort with monitoring technologies. No qualitative evidence was identified to inform this domain directly, but the GDG considered that most individuals would value a minimum level of monitoring sufficient to support safe insulin use.

The balance between benefits and harms was judged to probably favour more frequent self-monitoring. Despite the very low certainty of evidence, the consistent association with improved glycaemic control, absence of demonstrated harm and critical role of monitoring in insulin-treated diabetes supported a recommendation in favour of increased frequency.

Resource requirements were judged to be moderate and variable across settings. Increased frequency of fingerstick testing implies higher ongoing costs related to test strips and consumables, while use of rtCGM or isCGM may involve higher upfront and recurrent costs but inherently provides continuous or near-continuous data that exceeds the recommended minimum frequency. The GDG noted uncertainty regarding cost-effectiveness, particularly in low-resource and humanitarian settings, but considered that establishing a minimum frequency recommendation provides a pragmatic benchmark that can be adapted based on available technologies and resources.

The impact on health equity was judged to vary. More frequent monitoring may improve self-efficacy and glycaemic outcomes where supplies are available, but limited access to testing materials or technologies could exacerbate inequities in some settings. The GDG therefore emphasized that implementation of the recommendation should take into consideration the availability, affordability and sustainability of monitoring options.

Acceptability of more frequent self-monitoring was judged to be probably acceptable but variable. Feasibility was also judged to be probably acceptable, recognizing that implementation depends on reliable access to monitoring supplies, appropriate education and integration into routine clinical care.

Taking these considerations together, the GDG made a conditional recommendation in favour of frequent SMBG, reflecting very low certainty, small but consistent benefits, minimal identified harms and substantial contextual considerations related to feasibility, equity and resource availability. The GDG agreed to define frequent SMBG as three or more times per day to align with general feeding patterns and in accordance with the observed evidence.

In addition, no eligible studies were identified that evaluated the optimal timing of blood or interstitial glucose measurements or specific self-monitoring target values associated with improved outcomes. In the absence of such evidence, the GDG decided not to make recommendations on timing and target values.



3.4.3 Urine glucose testing

Recommendation 11

- Consider urine glucose testing in adults with type 1 diabetes when blood glucose testing is not available for self-monitoring.
  (conditional recommendation, low certainty)

Remarks

- Urine glucose testing is an alternative when blood glucose testing (e.g. fingerstick testing, real-time continuous glucose monitoring or intermittently scanned continuous glucose monitoring) is not available but should not replace blood glucose testing where blood glucose testing is accessible.

Summary of the evidence

Quantitative evidence

Characteristics of the evidence

The evidence informing the comparison between semi-quantitative non-invasive urine glucose monitoring (UGM) and fingerstick SMBG was derived from one RCT, conducted in the Russian Federation and published in 1994. The trial enrolled 121 participants with type 1 diabetes (UGM n = 61; SMBG n = 60), aged 15–45 years, receiving intensive insulin therapy. Follow-up was reported at 12 months and 24 months. The intervention consisted of urine glucose self-monitoring using semi-quantitative test strips, compared with conventional capillary blood glucose monitoring. The study was conducted prior to the availability of modern glucose monitoring technologies and diabetes education standards. Reporting of trial methods was limited, and the study was underpowered for most outcomes. Because only one trial contributed with data, meta-analysis was not possible, and findings were summarized narratively and presented in GRADE evidence profiles.

Outcomes

Urine glucose monitoring showed little to no difference in glycaemic control compared with fingerstick SMBG. Mean HbA1c levels were similar between groups over follow-up of 12 to 24 months, with an MD of 0.00% (95% CI -0.55 to 0.55). The confidence interval crossed the minimally clinically important difference in both directions, indicating substantial uncertainty regarding benefit or harm. Certainty of evidence for HbA1c was low, downgraded due to very serious imprecision and small sample size.

Evidence on hypoglycaemia was limited. For severe or serious hypoglycaemia, there was no clear difference between urine glucose monitoring and SMBG (RR 0.95, 95% CI 0.43 to 2.08). Absolute risk estimates were highly imprecise, and confidence intervals crossed thresholds for both benefit and harm. Data on mild, moderate or nocturnal hypoglycaemia were not reported. Certainty of evidence for hypoglycaemia outcomes was low, reflecting very serious imprecision and reliance on a single study.

The available evidence did not demonstrate a consistent difference between monitoring methods for DKA, but estimates were extremely imprecise (odds ratio 7.00, 95% CI 0.14 to 353.16), precluding reliable conclusions. Certainty of evidence for this outcome was low, due to very serious imprecision and few events.

All-cause mortality was uncommon and similar between groups (RR 0.98, 95% CI 0.06 to 15.37). Certainty of evidence for mortality was low, reflecting very wide confidence intervals and limited event numbers.

No evidence was identified for other outcomes, including time in target glucose range, glycaemic variability, quality of life, treatment satisfaction, adherence to monitoring method, adverse events related to monitoring or microvascular and macrovascular complications.

Overall, the certainty of the quantitative evidence for urine glucose monitoring compared with fingerstick SMBG was low across all critical outcomes, reflecting reliance on a single, randomized trial with very serious imprecision across all critical outcomes and limited outcome reporting.

See Web Annex A Table 13.1 for details of the evidence profiles.

Qualitative evidence

No qualitative evidence synthesis was commissioned to address values and preferences, acceptability or feasibility relevant to the PICO question. The considerations were informed by information reported in the included effectiveness studies, where available, combined with the experience and expertise of the GDG, including members with type 1 diabetes.

Economic evidence

Characteristics of the evidence

The economic evidence for urine glucose monitoring in adults with type 1 diabetes was limited to a single CBA conducted alongside a randomized clinical study by Starostina et al. (1994) in the Russian Federation. No additional cost-effectiveness, cost-utility or model-based economic evaluations comparing urine glucose monitoring with blood glucose self-monitoring (fingerstick testing or CGM) were identified.

The study was undertaken in a resource-constrained health system context and evaluated urine glucose testing as an alternative to blood glucose monitoring using capillary fingerstick testing. The analysis compared direct costs of monitoring strategies, including the costs of test strips, meters, lancets and related consumables, as well as downstream health-care utilization associated with diabetes management.

The economic analysis was conducted alongside clinical follow-up and reflected real-world prices and availability of monitoring supplies in a transition-economy setting. A simple sensitivity analysis was reported, showing net savings for urine glucose self-monitoring under alternative strip-price assumptions.

Outcomes

In this single cost-benefit analysis, urine glucose self-monitoring was associated with lower overall costs compared with blood glucose self-monitoring using fingerstick testing. The analysis reported net cost savings of US$ 132 per participant in the urine glucose self-monitoring group, compared with net costs of US$ 686 per participant in the blood glucose self-monitoring group over the study period.

Cost differences were driven primarily by the lower acquisition costs of urine glucose test strips compared with blood glucose test strips, as well as reduced expenditure on associated consumables such as lancets and meters. The study also considered downstream savings related to discontinuation of ineffective or unnecessary diabetes medications, which contributed to the overall cost advantage observed with urine glucose self-monitoring.

A simple sensitivity analysis reported by the authors indicated that urine glucose self-monitoring remained cost-saving under alternative price assumptions, particularly when the unit cost of urine glucose test strips was reduced. However, the analysis did not explore uncertainty systematically, and no probabilistic sensitivity analyses were conducted.

The study did not report health outcomes in terms of QALY, nor did it assess long-term diabetes-related complications or costs beyond the trial follow-up period. As a result, the economic findings are limited to short-term cost comparisons within the specific historical and health-system context in which the study was conducted.

Overall, the available economic evidence suggests that urine glucose self-monitoring may be cost-saving compared with blood glucose self-monitoring in a resource-constrained setting. However, confidence in this finding is limited by reliance on a single, older study, absence of contemporary economic modelling and limited generalizability to current practice.

See Web Annex B Table 4 for details of the economic studies.

Rationale for judgement

The GDG concluded that it would consider urine glucose monitoring only in settings where blood glucose testing is unavailable. Effective monitoring is essential for safe insulin use, but the GDG recognized that access to fingerstick blood glucose testing or CGM is uneven across settings, particularly in low-resource, emergency and humanitarian contexts.

The GDG judged that the desirable effects of urine glucose monitoring are trivial. Available evidence does not demonstrate clinically meaningful improvements in glycaemic control or hypoglycaemia outcomes compared with blood glucose monitoring. Urine glucose testing provides only indirect and delayed information on glycaemic status, cannot warn of hypoglycaemia and has limited sensitivity at lower glucose levels. Its primary benefit lies in the possibility to simultaneously detect ketones when dipsticks are used and in offering some insight into blood glucose trends when blood glucose testing is not available.

The undesirable effects were judged to be uncertain to small. No consistent safety concerns were identified, but reliance on urine glucose testing may delay recognition of periods of moderate but harmful hyperglycaemia and cannot detect hypoglycaemia, which is a critical limitation for people using insulin. These risks were considered context-dependent and more relevant if urine testing were used as a substitute for blood glucose testing when the latter is available.

The overall certainty of the evidence was judged to be low, reflecting reliance on a single randomized trial, imprecision and limited outcome reporting.

The GDG judged that how people value the critical outcomes shows minor variability. People with type 1 diabetes generally value having some form of feedback on glycaemic status, particularly when alternatives are unavailable. However, preferences are likely to favour blood glucose testing when accessible, given its greater accuracy and clinical usefulness.

Overall, the balance between benefits and harms was judged to favour blood glucose monitoring. Urine glucose monitoring does not offer comparable clinical benefit and carries important limitations, but may be preferable to no monitoring at all when blood glucose testing is unavailable.

The GDG judged the resource requirements to favour urine glucose monitoring, with large potential cost savings compared with blood glucose testing. Evidence from a single cost-benefit analysis conducted in a resource-constrained setting suggested that urine glucose monitoring was associated with cost savings compared with blood glucose self-monitoring. However, the GDG judged the certainty of evidence for cost-effectiveness to be uncertain due to reliance on a single, older study and lack of contemporary economic evaluations.

The impact on health equity was judged to vary depending on the setting. In contexts where blood glucose testing is unavailable or unaffordable, urine glucose monitoring may support more equitable access to some form of monitoring. Conversely, preferential use of urine testing in settings where blood glucose monitoring is available could exacerbate inequities by offering a lower-quality alternative.

Urine glucose monitoring was judged acceptable to people with type 1 diabetes and feasible to implement because of its simplicity and minimal supply requirements.

Finally, the GDG made a conditional recommendation in favour of urine glucose monitoring only when blood glucose testing is not available, reflecting low certainty, trivial clinical benefit compared with fingerstick monitoring, substantial resource considerations and important contextual and equity factors.



4 Implementation considerations



The recommendations in this guideline have been developed from a global public health perspective, recognizing that type 1 diabetes requires lifelong access to insulin, glucose monitoring and appropriate clinical support to prevent acute and long-term diabetes-related complications. Implementation will need to be adapted to the national health system, financing, regulatory frameworks and workforce capacity.

Most recommendations in this guideline are conditional and allow flexibility in clinical application. Their implementation should therefore be individualized at both the policy and service-delivery levels, taking into account available resources, existing service models and national standards of care. Countries should engage policy-makers, clinicians, procurement agencies, civil society and people with type 1 diabetes in adaptation and roll-out of these recommendations.

4.1 Health policy and system considerations

- Insulin therapy and glucose monitoring are essential components of care for adults with type 1 diabetes. Ensuring free access to these services at the point of care is consistent with the goals of universal health coverage, which seeks to guarantee that all individuals receive essential health services without financial hardship.

- Strengthening primary health care (PHC) systems is central to effective diabetes management. Many aspects of insulin initiation, titration, glucose monitoring interpretation and routine follow-up can be delivered in PHC settings, where workforce capacity and referral pathways are adequately developed and supported.

- Insulin remains a life-saving and non-substitutable medicine for people with type 1 diabetes. Countries should ensure that insulin is included in national essential medicines lists and is available at primary and referral levels of care. Reliable procurement, quality assurance and supply chain management systems are critical to prevent stock-outs.

- Access to glucose monitoring technologies, including fingerstick SMBG, rtCGM and isCGM, should be considered within national regulatory and financing frameworks. Monitoring supplies, including test

strips and sensors, are integral to safe insulin use and should be incorporated into national procurement and financing mechanisms.

- Given the conditional nature of several recommendations, countries may adopt phased or differentiated implementation strategies. Decisions regarding adoption and scale-up of specific insulin formulations or monitoring technologies should consider resource availability, regulatory approval status, workforce capacity and health system readiness.

- The cost of insulin and glucose monitoring supplies remains a significant barrier globally. Implementation may require strengthening public financing mechanisms, inclusion of insulin and monitoring supplies in national insurance benefit packages and development of sustainable procurement strategies.

- The relative cost and local availability of different insulin formulations, including premixed versus separate NPH and regular human insulin, vary substantially across settings. Procurement decisions should take into account local availability, patient-level costs and supply continuity, as costs may differ between countries and health system contexts.

4.2 Workforce considerations

- Build and sustain workforce capacity in competencies related to safe and effective insulin therapy including starting insulin, titrating doses of insulin, interpreting glucose data and preventing and managing hypoglycaemia and DKA.

- Training programmes should support skills in:
  - insulin dose adjustment based on glucose monitoring results
  - interpretation of SMBG and/or CGM data
  - HbA1c interpretation and individualization of targets
  - recognition and management of hypoglycaemia
  - recognition and management of DKA
  - preparation and administration of self-mixed (split-mix) insulin regimens

- Consider task-sharing approaches in settings with workforce shortages, with appropriate training and supervision mechanisms in place.

- Education and training to support safe use of insulin and glucose monitoring technologies are important components of effective implementation. Standardized competency frameworks and training curricula may support consistent implementation and reduce unwarranted variation in care. Integration of type 1 diabetes management into broader noncommunicable disease (NCD) training platforms may improve sustainability and system coherence.

- Inform health workers that intensified insulin therapy can be delivered using various injection devices, including syringes, insulin pens and cartridges, and that the choice of device should be guided by local availability and patient preference. Training should not assume availability of any single device type.

4.3 Service delivery considerations

- Clear referral pathways between primary care, specialist services and emergency care are essential for safe diabetes management. Service delivery models should ensure continuity of care, routine follow-up and timely management of complications.

- Implementation requires reliable access to insulin, HbA1c testing, as recommended elsewhere in this guideline, blood glucose monitoring supplies, and, where feasible, CGM technologies. Laboratories and point-of-care testing systems should meet appropriate quality standards.

- When CGM technologies are used, health workers should ensure that individuals understand how to operate the device and interpret glucose data in the context of their insulin regimen.

- Interruptions in insulin or monitoring supplies undermine implementation and increase the risk of acute complications. Strengthening cold-chain systems, inventory management and procurement forecasting is essential. Service delivery planning should prioritize uninterrupted access to insulin and monitoring supplies.

- Where intensified insulin therapy is in use, health-care providers should have contingency plans to enable rapid transition to simpler fixed-dose regimens in the event of interruptions in insulin or associated supplies availability. Such planning is particularly important in emergency and humanitarian settings where reliable access to insulin, injection devices and glucose monitoring cannot be consistently assured.

- When switching adults between premixed and self-mixed insulins, health workers should provide people with type 1 diabetes and their carers with education on dosing, timing of injections in relation to meals and recognizing and managing hypoglycaemia. When introducing premixed insulins in settings previously relying on self-mixed regimens, health-care providers should ensure that the capacity for self-mixing is maintained where clinically indicated.

- Adapt the timing of long-acting insulin analogues to individual patient circumstances, including work schedules, sleep patterns and daily routines. Health workers should not routinely restrict patients to a single preferred timing and should be aware that flexibility in timing is clinically acceptable.

4.4 Equity and special settings considerations

- Significant inequities persist in access to insulin and monitoring technologies, particularly in low-resource, rural, fragile and humanitarian settings. Implementation efforts should prioritize minimum standards of care, including reliable access to insulin and basic blood glucose monitoring.

- Special attention should be given to minimizing financial hardship, geographic barriers and discrimination in access to care. Policy development should actively involve people with type 1 diabetes to support equitable implementation.

- In settings with constrained resources, implementation may require prioritization of essential elements of care, while progressively strengthening access to additional technologies as capacity allows.

- The requirement for more injection devices and more frequent glucose monitoring associated with intensified insulin regimens may disproportionately affect individuals who pay for supplies out of pocket, potentially widening inequity in access to optimal care. Financing mechanisms and procurement policies should seek to mitigate this barrier.

- In humanitarian and emergency settings, access to insulin type and formulation is often determined by donation and supply availability rather than clinical preference. Recommendations on insulin regimen type should be implemented with the recognition that clinical teams in these settings may need to adapt the regimen to whatever insulin is available at the time.



5 Research gaps



The guideline development process identified important limitations in the certainty, scope and applicability of the available evidence across multiple PICOs. In several areas, recommendations were informed by low- or very low-certainty evidence (e.g. short-term RCTs, small observational studies or model-based economic analyses). In some domains, including re-classification and aspects of self-monitoring, eligible studies were extremely limited or absent.

Future research should include long-term cohort studies, registry-based analyses, pragmatic implementation research, independent economic evaluations and qualitative studies exploring patient and provider perspectives. Particular attention is needed to ensure representation from LMICs, fragile and humanitarian settings, and populations underrepresented in existing trials.

5.1 Cross-cutting evidence limitations

Several methodological gaps were observed consistently across PICOs.

Most randomized trials evaluating insulin therapies, delivery devices and glucose monitoring technologies were conducted in high-income settings, with minimal participation from LMICs and no studies from humanitarian contexts. This concentration limits generalizability and weakens the evidence base for global guidance.

Follow-up duration in many trials was relatively short, typically between 24 and 52 weeks. As a result, there is limited direct evidence linking specific insulin formulations, monitoring methods or delivery devices to long-term diabetes-related complications, such as microvascular and macrovascular diseases, mortality or sustained reductions in DKA and hypoglycaemia.

Across PICOs, patient-reported outcomes, including quality of life, treatment satisfaction, perceived burden of monitoring and fear of hypoglycaemia, were inconsistently reported and frequently rated as low or very low certainty. Future qualitative research on values and preferences, feasibility, equity or human rights considerations involving people living with type 1 diabetes, caregivers and health-care providers across diverse settings would strengthen future updates of the guideline.

Economic evidence was predominantly model-based, frequently manufacturer funded and largely derived from high-income countries. Assumptions about reductions in hypoglycaemia, HbA1c and long-term diabetes-related complications were often key drivers of the modelling for the cost-effectiveness conclusions. Independent evaluations and real-world cost analyses from LMIC settings are needed to strengthen confidence in economic findings.

5.2 Diagnosis and classification of type 1 diabetes

Evidence supporting biomarker use for diagnosis in adults was derived from non-randomized studies and was rated as very low certainty. Substantial heterogeneity in assay methods, thresholds and reference standards precluded pooled analysis, and no studies evaluated the impact of biomarker-informed diagnosis on clinical outcomes such as access to appropriate therapy, prevention of DKA or long-term diabetes-related complications.

Prospective diagnostic cohort studies using standardized biomarker definitions and consistent reference standards are needed. Given that the presence and titre of individual biomarkers depend on the time since diagnosis of diabetes, studies conducted in populations of various durations of diabetes are needed to inform decisions on the choice of diagnostic biomarker at different stages of type 1 diabetes natural history. In addition, research evaluating whether biomarker-informed classification improves clinical decision-making, reduces acute complications or alters long-term disease trajectories would strengthen future guidance.

Re-classification of diabetes type remains an area of profound uncertainty, as evidence was limited to a single small study. Robust prospective studies are required to develop evidence-based recommendations in this domain.

5.3 Insulin therapies

Randomized trials comparing rapid-acting insulin analogues with regular human insulin varied across rapid-acting insulin analogues type, with some showing small or no reductions in HbA1c compared to the control treatment. Where differences were seen between insulin analogues and human insulin, the HbA1c reductions were below thresholds generally considered clinically relevant. Several long-term diabetes-related complications, including microvascular and macrovascular diseases, were not directly evaluated.

Similarly, trials comparing basal insulin analogues with NPH insulin generally showed no clinically meaningful differences in HbA1c and mixed evidence regarding hypoglycaemia outcomes across analogues, with certainty frequently rated as low or very low. Follow-up duration was generally insufficient to assess long-term diabetes-related complications. Additionally, no trials directly comparing NPH insulin with insulin degludec were identified and such trials would provide evidence given the increasing use of ultra long-acting analogues.

The DCCT and its long-term observational follow-up in the EDIC study demonstrated the importance of intensive compared with less intensive insulin therapy for preventing or delaying microvascular and cardiovascular outcomes. However, contemporary trials directly linking specific insulin formulations to long-term diabetes-related complication outcomes remain lacking.

Evidence comparing premixed with self-mixed human insulin was limited to a single small trial reporting HbA1c only.

Future research relevant to this guideline includes:

- long-term comparative effectiveness studies examining complications and mortality;
- standardized definitions and reporting of hypoglycaemia and DKA;
- trials comparing premixed and self-mixed regimens with patient-reported and safety outcomes;
- pragmatic trials conducted in diverse health system settings;
- trials evaluating the utility of intensified regimens in the absence of possibility for frequent blood glucose self-monitoring;
- trials evaluating various insulin types and regimens in circumstances of food uncertainty;
- registry-based evaluations of real-world safety and effectiveness; and
- independent economic evaluations not reliant predominantly on manufacturer-funded modelling.

5.4 Insulin delivery methods

Evidence comparing insulin pens with syringes was derived largely from small crossover trials conducted several decades ago, with very low certainty evidence and short follow-up periods. HbA1c outcomes were reported and were not in favour of pens, but follow-up durations were insufficient to evaluate sustained glycaemic control or long-term diabetes-related complications. Data on sustained adherence, complications and environmental impact were absent.

Contemporary trials evaluating modern delivery devices, including smart pens, in varied resource settings would strengthen the evidence base. Research should also assess long-term adherence, patient-reported outcomes using validated instruments, insulin wastage and cost-effectiveness in diverse economic and health system contexts.

5.5 Clinical monitoring of glycaemic control

Evidence informing HbA1c monitoring frequency was limited to one RCT and two observational studies. Direct randomized comparisons of different HbA1c testing intervals were not available. Similarly, no trials directly compared specific HbA1c targets; instead, evidence was based on achieved glycaemic exposure in DCCT/EDIC.

Contemporary trials evaluating monitoring frequency and glycaemic targets in the context of applied insulin regimens and glucose monitoring technologies would provide greater certainty. Studies examining the impact of monitoring strategies on acute events, complications and quality of life are also needed.

5.6 Self-monitoring of glycaemia

Randomized trials evaluating CGM demonstrated small but consistent reductions in HbA1c and increases in time in range compared with fingerstick self-monitoring. However, evidence for severe hypoglycaemia, DKA and long-term outcomes was limited or low certainty. Quality of life data were sparse and inconsistently measured.

Evidence informing the frequency of self-monitoring was very limited and of very low certainty, derived from one randomized trial and two observational studies. No eligible studies evaluated optimal timing of glucose measurements or specific target values for self-monitoring.

Future research should include comparative trials evaluating monitoring frequency thresholds, assessment of monitoring patterns and acute complications, registry-based real-world analyses and studies conducted in LMIC and resource-constrained settings.

5.7 Urine glucose monitoring

Evidence for urine glucose monitoring was limited to a single randomized trial and one cost-benefit analysis conducted in a specific historical context. Contemporary comparative data are lacking.

Given its potential relevance in settings where blood glucose testing is not feasible, pragmatic implementation research examining safety, effectiveness and affordability in resource-constrained environments may be valuable.



6 Dissemination



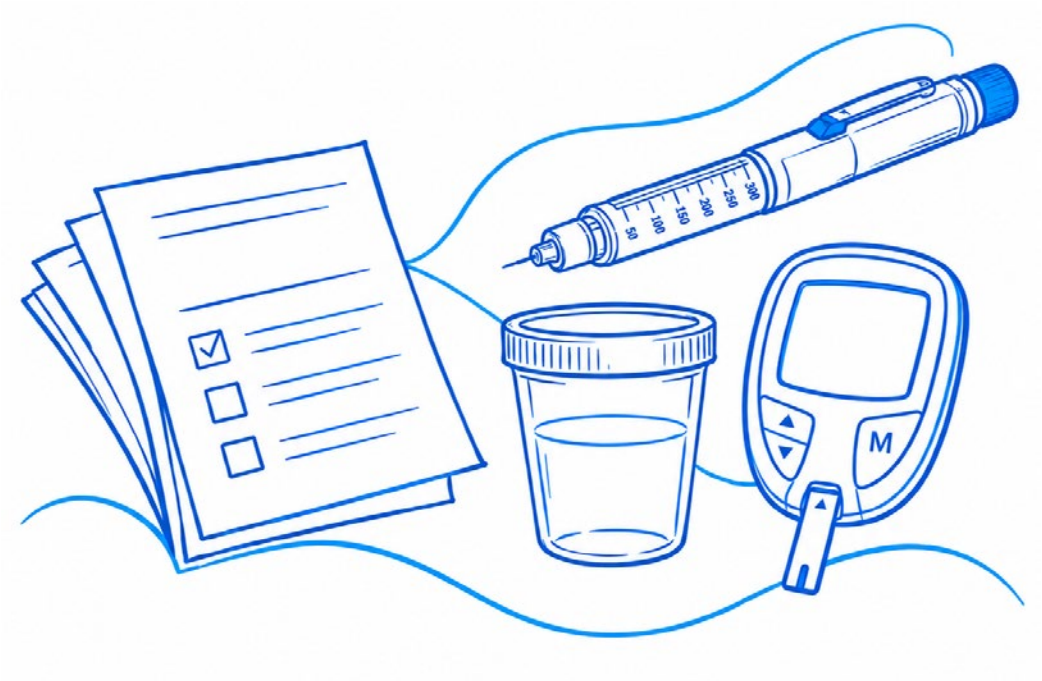
This guideline will be published on WHO's website and disseminated through WHO headquarters, Regional/Country Offices. The full guideline, executive summary, recommendation tables and web annexes containing evidence profiles will be made publicly accessible in accordance with WHO open-access policies. The executive summary and key messages will be translated into the six United Nations languages to facilitate global dissemination and uptake.

Dissemination will be closely aligned with the Global Diabetes Compact and its objective of improving prevention, diagnosis, treatment and monitoring of diabetes across the life course. In particular, the recommendations on insulin therapy, insulin delivery methods and glycaemic monitoring will support Member States in advancing equitable access to essential diabetes medicines and technologies and strengthening service delivery for people with type 1 diabetes. The guideline will be integrated into relevant WHO normative and technical platforms, including WHO guidance on NCDs, PHC strengthening, essential medicines and health technologies and quality of care initiatives.

WHO headquarters will collaborate with regional and country offices to support contextual adaptation and implementation. Dissemination activities will include technical briefings for ministries of health, professional associations and implementing partners; presentations at international scientific conferences and global NCD forums; and targeted webinars to support programme managers and clinicians. Implementation tools, including policy briefs and adaptation resources, may be developed to assist countries in prioritizing actions according to local epidemiology, health system capacity and resource availability.

Engagement with global and regional stakeholders will form a core component of dissemination. This includes collaboration with professional societies, diabetes advocacy groups, WHO collaborating centres, procurement and supply-chain partners, manufacturers and distributors of insulin and monitoring technologies and relevant United Nations agencies. The recommendations will also be promoted through the monthly WHO Global Diabetes Compact newsletter, disseminated to approximately 5000 stakeholders and shared with the Global Diabetes Compact Forum, established by WHO to foster advocacy, collaboration and the exchange of ideas to reduce diabetes risk and improve care for people with diabetes (over 180 stakeholders). The guideline will also be highlighted in connection with World Diabetes Day to support global awareness and dissemination. Particular attention will be given to ensuring that dissemination efforts reach LMICs, fragile settings and humanitarian contexts, where access to insulin and monitoring technologies remains even more constrained than other settings.

The guideline will also inform future updates of consolidated WHO NCD guidance and related technical documents. As new evidence emerges, particularly on long-term clinical outcomes, patient-reported outcomes and implementation experience in diverse settings, WHO will consider updates to this guidance and related products to support Member States.



7 Monitoring and evaluating guideline implementation

WHO may support Member States in monitoring implementation of the guidelines with approaches adapted to national context, priorities and capacity. Monitoring and evaluation should enable countries to assess the adoption, quality and outcomes of guideline uptake. Indicators could be adapted from existing WHO monitoring frameworks, including indicators relevant to noncommunicable diseases, universal health coverage recommendations and *Guidance on global monitoring for diabetes prevention and control: Framework, indicators and application.*

Where feasible, countries are encouraged to integrate monitoring within existing platforms for NCD surveillance and routine health information systems, rather than establishing parallel systems.



8 Updating the guideline

WHO will periodically review this guideline to determine whether new evidence and developments in type 1 diabetes care warrant updating. A formal review of the guideline will be undertaken within five to seven years of publication, or earlier if new evidence is identified that could substantially alter one or more recommendations. Any revision will follow established WHO procedures for guideline development and review. Updated recommendations will include the date of revision and the rationale for change.

Particular attention will be given to areas where recommendations were based on low or very low certainty evidence, where no recommendation was made due to insufficient evidence and where rapidly evolving technologies may generate new clinical data.

All technical documents developed during guideline preparation, including systematic reviews and evidence profiles, will be archived to facilitate efficient updating. WHO welcomes feedback from Member States, professional associations and stakeholders. Comments or suggestions for future updates may be submitted to GDC2030@who.int.



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Annexes



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Annex 2. GDG's contribution to recommendations

Table 7. Summary of individual GDG members' contributions to the formulation of recommendations

	Formulation of PICO questions	Formulation of recommendations 3a, 3b, 4a, 4b, 6, 7 and 8	Formulation of recommendations 1, 9, 10 and 11	Formulation of recommendations 2a, 2b and 5
Professor Amanda Adler	✔	✔	✔	✔
Dr Faria Afsana	✔	✔	✔	
Dr Elizabeth Bankah	✔	✔	✔	
Dr Abdul Basit	✔			✔
Professor Stéphane Besançon	✔	✔	✔	✔
Dr Justin Cirhuza Cikomola	✔			✔
Dr Omar Dirani	✔	✔	✔	
Dr Eddy Jean-Baptiste	✔	✔	✔	✔
Dr Sylvia Kehlenbrink	✔	✔	✔	
Dr Saurav Khatiwada	✔	✔	✔	✔
Professor Ko Ko	✔			✔
Dr Aime Manzi	✔	✔	✔	

	Formulation of PICO questions	Formulation of recommendations 3a, 3b, 4a, 4b, 6, 7 and 8	Formulation of recommendations 1, 9, 10 and 11	Formulation of recommendations 2a, 2b and 5
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Dr Marie E. McDonnell	✔	✔	✔*	✔
Professor Beatriz D'Agord Schaan	✔	✔	✔	✔
Professor Nikhil Tandon	✔	✔	✔	✔
Professor Marcello Tonelli	✔	✔	✔	✔
Ms Aigerim Zhaparova	✔	✔	✔	✔
Professor Zhiguang Zhou	✔	✔	✔	✔

**Member excluded from decision making/voting on recommendations 12 and 13 because of a declared interest.*

Annex 3. Declarations of interests

Table 8. Summary of GDG members' declarations of interests

Name	Interest declared	Management of conflicts
Professor Amanda Adler	None	Full participation
Dr Faria Afsana	None	Full participation
Dr Elizabeth Bankah	None	Full participation
Dr Abdul Basit	None	Full participation
Professor Stéphane Besançon	None	Full participation
Dr Justin Cirhuza Cikomola	None	Full participation
Dr Omar Dirani	None	Full participation
Dr Eddy Jean-Baptiste	None	Full participation
Dr Sylvia Kehlenbrink	None	Full participation
Dr Saurav Khatiwada	None	Full participation
Professor Ko Ko	None	Full participation
Dr Aime Manzi	None	Full participation
Ms Lucia Mbulaje	None	Full participation
Dr Marie E. McDonnell	Honoraria (US$ 1 000 annually) received from her employer (Harvard Medical School) for continuing medical education symposia. Her employer receives 5% of her salary from Dexcom for an ongoing research project.	Excluded from decision making; voting on recommendations related to self-monitoring of blood glucose. Can contribute as expert.
Professor Beatriz D'Agord Schaan	None	Full participation

Name	Interest declared	Management of conflicts
Professor Nikhil Tandon	None	Full participation
Professor Marcello Tonelli	None	Full participation
Ms Aigerim Zhaparova	None	Full participation
Professor Zhiguang Zhou	Has received advisory board honoraria in the equivalent of US$ 2 500 from Eli Lilly, Novo Nordisk, Sanofi, Dongbao, Ganli and United Laboratories. His institution has received the equivalent of US$ 280 000 from Dongbao, Ganli, United Laboratories for collaborative research on GLP-1 receptor agonists.	Personal financial interest not significant. Institutional research funding is not related to insulin use in type 1 diabetes. Full participation

Annex 4. Evidence-to-Decision (EtD) summaries

Table 9. Summary of judgements for using biomarkers for the diagnosis of type 1 diabetes in adults when the diagnosis is uncertain

EtD domain	Judgement
Benefits	Uncertain
Harms	Trivial/small
Overall certainty	Very low
Values and preferences	No important variability
Balance benefits to harms	Probably favours biomarkers
Resource considerations	Large
Certainty of evidence for resources	N/A
Cost-effectiveness	Probably favourable
Equity and human rights	Varies
Acceptability	Probably yes
Feasibility	Yes

Table 10. Summary of judgements for using biomarkers for reclassification of type 1 diabetes

EtD domain	Judgement
Benefits	Insufficient evidence
Harms	
Overall certainty	
Values and preferences	
Balance benefits to harms	

EtD domain	Judgement
Resource considerations	Insufficient evidence
Certainty of evidence for resources	
Cost-effectiveness	
Equity and human rights	
Acceptability	
Feasibility	

Table 11. Summary of judgements for insulin regimens (intensified versus conventional)

EtD domain	Judgement
Benefits	Large; moderate
Harms	Small
Overall certainty	Low
Values and preferences	Possibly important; probably no important uncertainty or variability
Balance benefits to harms	Favours intervention
Resource considerations	Moderate costs
Certainty of evidence for resources	N/A
Cost-effectiveness	Favours and probably favours intervention
Equity and human rights	Reduced
Acceptability	Yes and probably yes
Feasibility	Yes and probably yes

Table 12. Summary of judgements for using rapid-acting insulin analogues over human insulins

EtD domain	Judgement
Benefits	Trivial to small
Harms	Trivial
Overall certainty	Moderate
Values and preferences	Minor variability
Balance benefits to harms	Probably favours rapid-acting insulin analogues
Resource considerations	Large; but varies by country
Certainty of evidence for resources	N/A
Cost-effectiveness	Probably favourable; uncertain
Equity and human rights	May decrease equity; but could improve if availability widens
Acceptability	Yes
Feasibility	Variable

Table 13. Summary of judgements for insulin regimens (timing of bolus insulin)

EtD domain	Judgement
Benefits	Trivial
Harms	Uncertain
Overall certainty	Very low
Values and preferences	Possibly important; probably no important uncertainty or variability
Balance benefits to harms	Does not favour either
Resource considerations	Negligible costs and savings

EtD domain	Judgement
Certainty of evidence for resources	N/A
Cost-effectiveness	Does not favour either
Equity and human rights	No impact
Acceptability	Yes
Feasibility	Yes

Table 14. Summary of judgements for long-acting insulin analogues over intermediate-acting (NPH insulin)

EtD domain	Judgement
Benefits	Small to trivial (insulin detemir associated with reduced hypoglycaemia)
Harms	Trivial
Overall certainty	Moderate
Values and preferences	Minor variability
Balance benefits to harms	Overall favours either option; for insulin detemir probably favours insulin analogues
Resource considerations	Large; especially in LMICs; driven by product cost
Certainty of evidence for resources	N/A
Cost-effectiveness	Varies; probably favourable or uncertain overall; for detemir probably favourable
Equity and human rights	Probably reduces equity
Acceptability	Probably yes among people with type 1 diabetes; varies but probably yes among health-care providers
Feasibility	Variable

Table 15. Summary of judgements for insulin regimens (timing of basal insulin)

EtD domain	Judgement
Benefits	Trivial to uncertain (for all three comparisons)
Harms	Trivial to uncertain (for all three comparisons except for morning versus evening which included moderate harms for morning dose)
Overall certainty	Low to very low (flexible versus evening was only low)
Values and preferences	Possibly important; probably no important uncertainty or variability
Balance benefits to harms	Does not favour either
Resource considerations	Negligible costs and savings
Certainty of evidence for resources	N/A
Cost-effectiveness	Does not favour either
Equity and human rights	No impact
Acceptability	Yes
Feasibility	Yes

Table 16. Summary of judgements for insulin regimens (premixed versus self-mixed insulin)

EtD domain	Judgement
Benefits	Uncertain
Harms	Uncertain
Overall certainty	Very low
Values and preferences	Possibly important; probably no important uncertainty or variability
Balance benefits to harms	Uncertain

EtD domain	Judgement
Resource considerations	Moderate costs
Certainty of evidence for resources	N/A
Cost-effectiveness	Varies
Equity and human rights	Varies
Acceptability	Yes
Feasibility	Yes

Table 17. Summary of judgements for using pens over syringes and needles

EtD domain	Judgement
Benefits	Uncertain to moderate
Harms	Trivial
Overall certainty	Very low
Values and preferences	Minor variability
Balance benefits to harms	Equal or probably favours pens
Resource considerations	Moderate
Certainty of evidence for resources	N/A
Cost-effectiveness	Uncertain
Equity and human rights	May decrease or varies
Acceptability	Yes
Feasibility	Yes

Table 18. Summary of judgements for frequency of glycaemic control (HbA1c) monitoring

EtD domain	Judgement
Benefits	Small to moderate; uncertain
Harms	Trivial; uncertain
Overall certainty	Low
Values and preferences	Probably important variability or uncertainty
Balance benefits to harms	Probably favours increased frequency
Resource considerations	Moderate; varies
Certainty of evidence for resources	N/A
Cost-effectiveness	Probably favours increased frequency
Equity and human rights	May reduce or increase; varies
Acceptability	Probably yes
Feasibility	Varies; uncertain

Table 19. Summary of judgements for glycaemic control (HbA1c) targets

EtD domain	Judgement
Benefits	Large (some moderate)
Harms	Moderate (some large)
Overall certainty	Moderate (benefits and harms)
Values and preferences	Major variability and uncertainty
Balance benefits to harms	Favours lower target (may differ in emergency, humanitarian and older populations)
Resource considerations	Moderate
Certainty of evidence for resources	N/A

EtD domain	Judgement
Cost-effectiveness	Probably favours aiming for a lower HbA1c target
Equity and human rights	Could decrease; varies
Acceptability	Varies
Feasibility	Varies; probably yes; depending on setting and target value

Table 20. Summary of judgements for methods of self-monitoring of glycaemia compared to fingerstick testing

EtD domain	Real-time CGM (rtCGM)	Intermittently scanned CGM (isCGM/FGM)	Urine glucose monitoring
Benefits	Moderate to large	Moderate to large	Trivial
Harms	Trivial	Trivial	Uncertain to small
Overall certainty	Moderate	Moderate	Low
Values and preferences	Minor variability	Minor variability	Minor variability
Balance benefits to harms	Favours rtCGM	Favours isCGM	Probably favours SMBG
Resource considerations	Large costs	Large costs	Lower costs
Certainty of evidence for resources	N/A	N/A	N/A
Cost-effectiveness	High-income settings: probably favours LMICs; uncertain	High-income settings: probably favours LMICs; uncertain	Uncertain
Equity and human rights	Likely to decrease equity; varies by setting	Likely to decrease equity; varies by setting	Varies; may be relevant in humanitarian settings

EtD domain	Real-time CGM (rtCGM)	Intermittently scanned CGM (isCGM/FGM)	Urine glucose monitoring
Acceptability	Acceptable to adults with type 1 diabetes; health worker views may vary	Acceptable to adults with type 1 diabetes; health worker views may vary	Acceptable but variable
Feasibility	Yes; but varies by setting	Yes; but varies by setting	Yes

Table 21. Summary of judgements for using rtCGM versus isCGM

EtD domain	Judgement
Benefits	Small to moderate
Harms	Trivial
Overall certainty	Moderate
Values and preferences	Minor variability
Balance benefits to harms	Favours; probably favours
Resource considerations	Large; varies
Certainty of evidence for resources	N/A
Cost-effectiveness	Probably favours; could be small
Equity and human rights	Decrease equity; uncertain
Acceptability	People with type 1 diabetes: Yes; health-care professional: Yes; varies
Feasibility	Probably yes; yes

Table 22. Summary of judgements for frequency of self-monitoring of glycaemia

EtD domain	Judgement
Benefits	Moderate
Harms	Uncertain to trivial
Overall certainty	Very low
Values and preferences	Possibly important variability
Balance benefits to harms	Probably favours more frequent self-monitoring
Resource considerations	Moderate costs
Certainty of evidence for resources	N/A
Cost-effectiveness	Uncertain; probably favours if reduced long-term complications
Equity and human rights	Increase (self-efficacy); decrease (non-availability); varies
Acceptability	Probably yes; varies
Feasibility	Probably yes; but will vary

Web Annex A. GRADE evidence profiles

Guidelines on insulin use for type 1 diabetes in adults, including in emergency and humanitarian settings: GRADE evidence profiles https://doi.org/10.2471/B09968

Web Annex B. Summary of cost-effectiveness studies

Guidelines on insulin use for type 1 diabetes in adults, including in emergency and humanitarian settings: Summary of cost-effectiveness studies https://doi.org/10.2471/B09969

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