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Regular human insulins versus rapid-acting insulin analogues in children and adolescents with type 1 diabetes: a protocol for a systematic review with meta-analysis and Trial Sequential Analysis

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Abstract

Background Type 1 diabetes is a serious, chronic disorder with an increasing incidence among children and adolescents. Glycemic control in individuals with type 1 diabetes is better managed through a basal-bolus regimen with either regular human or rapid-acting insulin analogues administered as a bolus at mealtimes. Rapid-acting insulin analogues have been hypothesized to cause optimal glycemic control and less risk of hypoglycemic episodes compared to regular human insulins. However, this has never been systematically assessed in children and adolescents with type 1 diabetes. Therefore, this systematic review aims to assess the beneficial and harmful effects of regular human insulins versus rapid-acting insulin analogues in children and adolescents.

Methods This is a protocol for a systematic review. A search in major medical databases (e.g., MEDLINE, EMBASE, CENTRAL) and clinical trial registries will be performed by a search specialist. We will include published and unpublished randomized clinical trials comparing regular human insulins versus rapid-acting insulin analogues (lispro, aspart, or glulisine). Two review authors will independently extract data and conduct risk of bias assessments. Primary outcomes will be severe hypoglycemia, ketoacidosis, and serious adverse events. Secondary outcomes will be quality of life, HbA1c, and non-serious adverse events. Data will be analyzed using fixed-effect meta-analyses, random-effects meta-analyses, and Trial Sequential Analysis. Several subgroup analyses are planned. Risk of bias will be assessed with the Cochrane Risk of Bias tool—version 2, an eight-step procedure will be used to assess if the thresholds for clinical significance are crossed, and the certainty of the evidence will be assessed by Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

Discussion The beneficial and adverse effects of regular human insulins versus rapid-acting insulin analogues have not been systematically assessed in children and adolescents. There is a need for a comprehensive systematic review of the current evidence.

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Keywords Type 1 diabetes, Regular human insulins, Rapid-acting insulin analogues, Children, Adolescents, Meta-analysis

Introduction

Description of the condition

Type 1 diabetes represents a critical and chronic health condition, characterized by a rising incidence rate and marked geographic disparities [1–3]. In children and adolescents, type 1 diabetes accounts for more than 85% of diabetes cases with the highest incidence in children aged 10–14 years [4, 5].

Type 1 diabetes is characterized by autoimmune destruction of the pancreatic β-cells producing insulin for the body [6, 7]. The progression rate varies depending on immune system activity and islet cell autoimmunity [6, 7]. Although the exact cause of this autoimmune response remains elusive, it is believed to result from a combination of genetic predisposition and environmental factors [8, 9]. This leads to the development of multiple islet autoantibodies (stage 1) and subsequent pre-clinical dysregulation of blood glucose levels (stage 2) [8, 9]. This autoimmune destruction results in complete insulin deficiency and hyperglycemia (stage 3), all resulting in full establishment of the disease (stage 4) [8, 9]. At stages 3 or 4 type 1 diabetes, individuals typically present with symptoms, including polyuria (excessive urine production), polydipsia (excessive thirst or excess drinking), weight loss, fatigue, and abdominal pain [6]. Frequencies of experiencing diabetic ketoacidosis at onset range from approximately 15 to 70% in Europe and North America, being as high as 80% in low-resourced countries [10–12].

The diagnosis of type 1 diabetes is associated with short-term and long-term complications [6]. Although clinical manifestations of diabetes-related vascular complications are uncommon during childhood and adolescence, early functional and structural vascular abnormalities may begin to emerge relatively soon, within just a few years following the diagnosis of type 1 diabetes [13]. In the short term, the lack of insulin production and glycemic control in type 1 diabetes increases the risk of ketoacidosis and possibly death if the supply of insulin is not restored [6]. In the long term, diabetes is associated with complications related to microvascular diseases including retinopathy, nephropathy, and neuropathy and macrovascular diseases including cardiovascular, cerebrovascular, and peripheral vascular diseases [6].

Blood sugar levels must be measured frequently for monitoring type 1 diabetes [14]. There is a wide selection of tools to assess glycemia, including self-monitored capillary blood glucose, glycosylated hemoglobin A1c (HbA1c), and continuous glucose monitors [6]. HbA1c serves as a biomarker, reflecting the average plasma glucose over the previous 8–12 weeks [14]. This 3-month timeframe is chosen due to the typical lifespan of a red blood cell [14]. In diabetes, HbA1c is therefore used as an evaluation method for monitoring glycemic control during treatment [14].

Description of the interventions

In the management of type 1 diabetes, the aim is to avoid the above mentioned short-term and long-term complications [6]. In children and adolescents with type 1 diabetes, this is typically managed through education on nutrition (e.g., carbohydrate counting and nutritional advice) and insulin treatment [15]. The insulin is provided through insulin syringes, insulin pens, or insulin pumps [15]. To mimic the natural levels of insulin, basal insulin is often combined with a bolus of insulin for meals [15]. The bolus of insulin administered at mealtimes may be either regular human insulins (also called "short-acting insulins") or rapid-acting insulin analogues [16]. Currently, the rapid-acting insulin analogues approved by the US Food and Drug Administration (FDA) are insulin lispro, insulin aspart, and insulin glulisine [17].

In addition to the short-term and long-term complications of diabetes, the administration of insulin is also associated with possible complications [6]. A potential complication of insulin treatment is the risk of hypoglycemia [18]. The insulin administration becomes more complex during periods of illness and physical activity or lack of access to self-blood glucose monitoring, complicating the management of type 1 diabetes further [19].

The rapid-acting insulin analogues have different molecular structures than regular human insulins, resulting in different pharmacokinetic characteristics and possibly different occurrences of adverse effects (Table 1) [20]. Compared to regular human insulins, insulin lispro has reversed amino acid proline at B28 and lysine at B29, insulin aspart has replaced proline at B28 with aspartic acid, and insulin glulisine has replaced asparagine at B3 and glutamic acid at B29 with lysine [21]. The regular human insulins have a slower and longer lasting rise in blood concentration compared to the rapid-acting insulin analogues [20], which have been hypothesized to cause of hypoglycemic episodes [22]. Instead, the faster rise and shorter duration of action of rapid-acting insulin analogues may better mimic the normal insulin levels following a

Table 1 Pharmacokinetics of short-acting insulin and rapid-acting insulin analogues [21]

	Onset of action	Peak effect	Duration of action	Timing of dose
Short-acting insulins				
Regular human insulins	~30 min	1.5 to 3.5 h	7 to 8 h	30 to 45 min before meal
Rapid-acting insulin analogues				
Insulin lispro	~15 min	30 to 70 min	2 to 5 h	15 min before or immediately after meal
Insulin aspart	10 to 20 min	1 to 3 h	3 to 5 h	5 to 10 min before meal
Insulin glulisine	10 to 20 min	~55 min	~6 h	15 min before or within 20 min after meal

meal, potentially reducing the risk of the hypoglycemic episodes [20]. In addition, the timing of administration differs between regular human insulins and rapid-acting insulin analogues [20]. The most commonly recommended interval between short-acting regular human insulin and a meal is 30 to 45 min, while rapid-acting insulin analogues are recommended to administer closer to mealtimes [20, 21].

Previous evidence

Previous reviews have assessed the beneficial and adverse effects of regular human insulins versus rapid-acting insulin analogue in adults [22–24]. A Cochrane review from 2016 found slightly better glycemic control with rapid-acting insulin analogues compared with regular human insulins, but there is not enough information on the difference in severe hypoglycemic episodes [22]. Two other systematic reviews with meta-analyses found similar results in adult populations [23, 24].

A systematic review from 2019 assessed regular human insulins versus rapid-acting insulin analogues in children, adolescents, and adults [25]. This review found no difference in glycemic control or hypoglycemic episodes [25]. However, only five randomized clinical trials with children and adolescents were included [25]. Another systematic review from 2018 assessed regular human insulins versus rapid-acting insulin analogues in special populations, including children and adolescents [26]. Here, eight randomized clinical trials with children and adolescents were included [26]. This review performed no meta-analyses on glycemic control and showed no difference in severe hypoglycemic episodes [26]. However, it was limited by not publishing a protocol beforehand, not searching all relevant databases, not employing trial sequential analyses methods to control for random errors, not assessing risks of bias, and not assessing the certainty of evidence using GRADE [26].

No systematic review has yet assessed regular human insulins versus rapid-acting insulin analogues solely in children and adolescents.

Does strict glycemic control lead to fewer complications?

Previous reviews have primarily focused on surrogate outcomes such as glycemic levels as the target of diabetes treatment [25–27]. These biomarkers are used as replacements for patient-important outcome measures such as short-term and long-term complications, including death, loss of vision, or hospitalizations [28, 29]. This is often done to reduce the follow-up time and costs of the clinical trials [30]. However, if surrogate outcomes should be used, they must be validated as an indicator of the clinical patient-important outcomes, as positive shifts in surrogate outcomes do not necessarily translate to clinically meaningful benefits [31–33].

A systematic review with meta-analyses published in 2014 assessed the effects of targeting intensive versus conventional glycemic control on all-cause mortality, cardiovascular mortality, severe adverse events, macrovascular complications, nephropathy and end-stage renal disease, and severe hypoglycemia [34]. This review found that intensive treatment programs compared to conventional treatment did not influence the risk of death, cardiovascular mortality, or severe adverse events [34]. Intensive treatment programs decreased the risk of macrovascular complications, nephropathy, and end-stage renal disease but increased the risk of severe hypoglycemia [34].

Included in the systematic review from 2014, The Diabetes Control and Complications Trial, a pivotal multicenter study conducted in North America from 1983 to 1993, randomized 1441 individuals aged 13 and above with diabetes, including 195 adolescents aged 13 to 17 years, to assess the impact of intensive glycemic control on long-term complications [35]. This trial showed a reduction of retinopathy, microalbuminuria, and neuropathy with strict glycemic control compared to conventional, moderate glycemic control [35]. Still, the strict glycemic intervention also led to a two- to

threefold increased risk of hypoglycemia [35]. The reductions in retinopathy and nephropathy were consistent in subgroup analyses on adolescents compared to adults, but these subgroup analyses were presumably underpowered [35]. Besides these subgroup analyses, no further information on glycemic control as surrogate outcome for short-term and long-term complications in children and adolescents with type 1 diabetes was available [36–38].

There is limited validation of glycemic control as a validated surrogate outcome for patient-important outcome measures in children and adolescents with type 1 diabetes. Therefore, current systematic reviews should include both clinical patient-important outcomes such as short-term and long-term complications of diabetes and complications of insulin treatment and measures of glycemic control.

With an increasing incidence of type 1 diabetes in children and adolescents and multiple possible interventions available for glycemic control, there is a need for a comprehensive overview of the current evidence. The objective of this systematic review is to assess the beneficial and adverse effects of regular human insulins versus rapid-acting insulin analogues in children and adolescents. The focus will be short-term and long-term complications of diabetes and possible complications of insulin treatment.

Methods

The protocol is reported following the reporting guideline provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement [39, 40] (Additional file 1) and is registered in the PROSPERO database.

Criteria for considering studies for this review

Types of studies

We will include randomized clinical trials irrespective of publication year, status, and language. We will include cross-over trials using only data from the first period of the trial. We will not include quasi-randomized trials, cluster-randomized trials, non-randomized studies, or studies with continuous changes in intervention or control.

Types of participants

Children and adolescents (less than 18 years old) with the diagnosis of type 1 diabetes (as defined by trialists) will be included.

Types of interventions

Experimental group As experimental interventions, we will accept regular human insulins, regardless of method of delivery (syringe, pen, or pump).

Control group As control interventions, we will accept rapid-acting insulin analogues (insulin lispro, insulin aspart, or insulin glulisine), regardless of method of delivery (syringe, pen, or pump).

Cointerventions We will accept any cointerventions, if these are planned to be delivered similarly in the experimental and control groups.

Outcome measures

Primary outcomes

1. Severe hypoglycemia (as defined by trialists).
2. Ketoacidosis (as defined by trialists).
3. Serious adverse events. We will use the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolonging of existing hospitalization, and resulted in persistent or significant disability or jeopardized the participant [41]. If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term "serious adverse event." If the trialists do not use the ICH-GCP definition or the term serious adverse event, we will also include the data if the event clearly fulfills the ICH-GCP definition of a serious adverse event. We will exploratorily assess each type of serious adverse event separately.

Secondary outcomes

1. Quality of life (as defined by trialists).
2. HbA1c.
3. Non-serious adverse events (will be reported and analyzed separately). Non-serious adverse events will be any adverse event not fulfilling the definition of a serious adverse event (see above).

Exploratory outcomes

1. All-cause mortality
2. Postprandial blood glucose (as defined by trialists)
3. Continuous blood glucose monitoring (as defined by trialists)
4. Retinopathy (as defined by trialists)
5. Nephropathy (as defined by trialists)
6. Cardiovascular complications (as defined by trialists)
7. Hospitalizations (as defined by trialists)
8. Changes in height
9. Changes in weight
10. Quality of life of the parents/caregivers (any valid continuous scale, e.g., 36-Item Short Form Survey) [42]
11. Cost of intervention
12. Nocturnal hypoglycemia

Assessment time points

We will assess all outcomes at maximum follow-up.

Search methods for identification of studies

Electronic searches

We will search Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LI-LACS), Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index—Science (CPCI-S), and the Health Technology Assessment (HTA) to identify relevant trials. We will search all databases from their inception to the present. Trials will be included irrespective of language, publication status, publication year, and publication type. For a detailed search strategy for all electronic searches, see supplementary material (Additional file 2).

Searching other resources

The reference lists of relevant trial publications will be checked for any unidentified randomized clinical trials. To identify unpublished trials, we will search clinical trial registries (e.g., clinicaltrials.gov, clinicaltrialregister.eu, who.int/ictrp, chictr.org.cn) of Europe and USA.

If we identify these, we will also include unpublished and gray literature trials and assess relevant retraction statements and errata for included trials. We will search preprint servers (bioRxiv, medRxiv) and contact relevant pharmaceutical companies for unpublished trials or additional data.

Data collection

We will perform and report the review as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [43]. Analyses will be performed using Stata version 17 (StataCorp LLC, College Station, TX, USA) [44] and Trial Sequential Analysis [45, 46].

Selection of randomized clinical trials

Two review authors will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publications, and two review authors will independently screen the full texts and will record reasons for the exclusion of the ineligible studies. The same two review authors will resolve disagreements through discussion, or if required, they will consult a third author (JCJ).

Data extraction and management

Two review authors will independently extract data from included trials in a predefined form. Disagreements will be resolved by discussion with a third author (JCJ). The two review authors will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximize data extraction, correct bias assessment). Each trial will be named after the first author and year of the primary publication, and all secondary publications will be classified under that name. We will contact the trial authors by email to specify any missing data, which may not be reported sufficiently or at all in the publication.

Trial characteristics

We will extract the following data: bias risk components (as defined below), trial design (parallel, factorial, or crossover), number of intervention groups, length of follow-up, estimation of sample size, diagnostic criteria, income setting (as per World Bank classification) [47], inclusion and exclusion criteria, method of measuring, and definition of outcomes.

Participant characteristics

We will extract the following data: number of randomized participants, number of analyzed participants, HbA1c at baseline, age range (mean or median), sex ratio, and ethnicity.

Experimental intervention characteristics

We will extract the following data: dose, administration time, and way of application (syringe, pen, or pump).

Control intervention characteristics

We will extract the following data: type of control, dose, administration time, and way of application (syringe, pen, or pump).

Outcomes

All outcomes listed above will be extracted from each randomized clinical trial.

Notes

We will search for information regarding industry funding of either personal or academic activities for each trial author. We will judge a publication at high risk of for-profit bias if a trial is sponsored by the industry or if just one author has affiliation to the industry [48]. We will note in the "Characteristics of included studies" table if outcome data were not reported in a usable way. Disagreements will be resolved through discussion, or if required, we will consult with a third author (JCJ).

Assessment of risk of bias in the included studies

Our bias risk assessment will be based on the Cochrane Risk of Bias tool—version 2 (RoB 2) as recommended in The Cochrane Handbook of Systematic Reviews of Interventions [49]. We will evaluate the methodology in respect of the following bias domains:

- Bias arising from the randomization process
- Bias due to deviation from intended interventions (effect of assignment to intervention)
- Bias due to missing outcome data
- Bias in measurement of outcomes
- Bias arising from selective reporting of results
- Overall assessment of risk of bias

We will assess the domains "deviations from intended interventions," "missing outcome data," "risk of bias in measurement of the outcome," and "risk of bias in selection of the reported result" for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. The overall risk of bias of a result or trial will be judged to be low if all domains are assessed at low risk of bias. If one or more domains are assessed at either some concerns or high risk of bias, the overall risk of bias will be assessed at high. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.

Differences between the protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the "Differences between the protocol and the review" section of the systematic review.

Measurement of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes.

Continuous outcomes

We will calculate the mean differences (MDs) and consider calculating the standardized mean difference (SMD) with 95% CI.

Dealing with missing data

We will use intention-to-treat data if provided by the trialists [50]. We will, as the first option, contact all trial authors to obtain any relevant missing data (i.e., for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes

We will primarily analyze scores assessed at maximum follow-up. If only changes from baseline scores are reported, we will analyze the results together with follow-up scores [51]. If standard deviations (SDs) are not reported, we will calculate the SDs using relevant trial data (e.g., *P* values), if possible. We will not use intention-to-treat data if the original report did not contain such data, per protocol data will then be used. In our best–worst-case and worst-best-case scenarios (see paragraph below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will primarily visually investigate forest plots for signs of heterogeneity. We will secondly assess the presence of statistical heterogeneity using I^2 statistic [49, 52, 53]. We will only conclude that the heterogeneity is high if the between trial variance translates to differences important to patients (based on the effect sizes defined by in the Trial Sequential Analysis, see below). We will investigate heterogeneity through subgroup analyses (see "Subgroup analyses and integration of heterogeneity" section below). We may ultimately decide that a meta-analysis should be avoided if heterogeneity is high [49].

Assessment of reporting biases

We will use a funnel plot to assess reporting bias if ten or more trials are included [49]. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e., a funnel plot assesses small study bias) [49]. From this information, we will assess possible reporting bias. For dichotomous outcomes, we will test asymmetry with the Harbord test [54] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1 [49].

Unit of analysis issues

We will only include randomized clinical trials. For trials using crossover design, only data from the first period will be included [49, 55]. There will therefore not be any unit of analysis issues. We will not include cluster randomized trials.

Data synthesis

Meta-analysis

We will undertake the meta-analyses according to the *Cochrane Handbook of Systematic Reviews of Interventions* [51], Keus et al. [56], and the eight-step assessment suggested by Jakobsen et al. [57]. We will use the statistical software Stata [44] to analyze data. We will assess our intervention effects with both a random-effects meta-analysis [58] and fixed-effect meta-analysis for each treatment comparison separately [59]. We will primarily report the most conservative point estimate of the two (highest *P* value) and consider the less conservative results a sensitivity analysis [57]. We will assess a total of three primary outcomes and consider a *P* value of < 0.025 (adjustment per recommendations by Jakobsen et al.) or less as the threshold for statistical significance [57]. We will investigate possible heterogeneity through subgroup analyses. We will use the eight-step procedure to assess if the thresholds for significance are crossed [57]. We will include only the relevant arms where multiple trial arms are reported in a single trial. If two comparisons are combined in the same meta-analysis, we will split the control group to avoid double-counting [49].

Trial Sequential Analysis

We wish to control the risks of both type I errors and type II errors. We will therefore perform Trial Sequential Analysis on all outcomes, in order to calculate the required information size (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries [45, 46, 60–66]. A more detailed description of Trial Sequential Analysis can be found in the Trial Sequential Analysis manual [46] and at http://www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction or a relative risk increase of 20%, an alpha of 2.5% for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will in the Trial Sequential Analysis use the observed standard deviation (SD), a mean difference equal to the observed SD/2, an alpha of 2.5% for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis.

Subgroup analyses and integration of heterogeneity

Subgroup analyses

We will perform the following subgroup analyses when analyzing the primary outcomes (severe hypoglycemia, ketoacidosis, and serious adverse events).

1) Trials at overall low risk of bias compared to trials at overall high risk of bias.
2) Trials with for-profit bias compared to trials without for-profit bias.
3) Trials with prepubertal participants (children) compared to trials with pubertal participants (adolescents).
4) Type of comparator (insulin lispro, insulin aspart, insulin glulisine).
5) Method of delivery (syringe, pen, or pump).
6) Trials performed in countries with high-income economies compared to trials performed in countries with middle- or low-income economies.

We will use the formal test for subgroup interactions in Stata [44]. We will perform any unanticipated subgroup analyses, if we identify these.

Sensitivity analysis

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on all primary and secondary dichotomous outcomes.

- Best–worst-case scenario: We will assume that all participants lost to follow-up in the experimental group had a beneficial outcome (no severe hypoglycemia, ketoacidosis, serious adverse event, or non-serious adverse event), and that all those participants lost to follow-up in the control group had a harmful outcome (severe hypoglycemia, ketoacidosis, serious adverse event, or non-serious adverse event).

- Worst-best-case scenario: We will assume that all participants lost to follow-up in the experimental group had a harmful outcome (severe hypoglycemia, ketoacidosis, serious adverse event, or non-serious adverse event), and that all those participants lost to follow-up in the control group had a beneficial outcome (no severe hypoglycemia, ketoacidosis, serious adverse event, or non-serious adverse event).

We will present results of both scenarios in our review. When analyzing continuous outcomes, a beneficial outcome will be the group mean plus two SDs of the group mean, and a harmful outcome will be the group mean minus two SDs of the group mean [57].

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis:

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute the mean SD from all included trials.

We will present results of this scenario in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results [57].

Summary of findings table

We will create a summary of findings table including each of the prespecified outcomes. We will use the five GRADE considerations (bias risk of the trials, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence [57, 67–69]. We will assess imprecision using Trial Sequential Analysis. We will justify all decisions to downgrade the certainty of the evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. Firstly, we will present our results in the summary of findings table based on the results from the trials with overall low risk of bias, and secondly, we will present the results based on all trials.

Discussion

This systematic review with meta-analyses and Trial Sequential Analysis of randomized clinical trials aims to assess the beneficial and adverse effects of regular human insulins versus rapid-acting insulin analogues in children and adolescents. Primary outcomes will be severe hypoglycemia, ketoacidosis, and serious adverse events. Secondary outcomes will be quality of life, HbA1c, and non-serious adverse events.

One of the strengths of our protocol is the methodological approach. The predefined methodology is based on Keus et al. [70], our eight-step assessment suggested by Jakobsen et al. [57], Trial Sequential Analysis [71], and GRADE assessment of the certainty of evidence [68, 72, 73]. Therefore, we consider both the risk of random errors and the risk of systematic errors. Furthermore, we increase the statistical power by pooling all rapid-acting insulin analogues as the control intervention. This also allows us to assess the relative effects of rapid-acting insulin analogues on regular human insulins. Even though we expect mainly short-term results, we will assess all outcomes at maximum follow-up. This allows differences in the long-term effects of the interventions to be included in our results.

Our protocol also has some limitations. The primary limitation is the risk of identifying a limited number of randomized clinical trials and thereby reducing the power of our results. Furthermore, the included trials may only have a short follow-up time. As pharmacological treatment in children and adolescents with type 1 diabetes is a lifelong treatment, these trial results of short intervention periods may not resemble how the interventions are used in the clinical practice. Also, there is a potential for high statistical heterogeneity due to the pooling of rapid-acting insulin analogues. To minimize this limitation, we have planned a subgroup analysis comparing regular human insulins to the different kinds of rapid-acting insulin analogues. This creates another possible limitation which is the number of subgroup analyses. This increases the risk of type I errors. Our threshold for significance has not been adjusted according to the number of secondary outcomes, exploratory outcomes, or subgroup analyses. In addition, although not considered as a primary outcome in our review, HbA1c represents only an approximate measure of glucose control; it does not address short-term glycemic variability or hypoglycemic events. For example, HbA1c values may be similar for individuals with highly variable glucose readings, including frequent peaks and troughs, for those with consistently stable glucose levels. Therefore, glycemic control will also be assessed through postprandial blood glucose or continuous blood glucose monitoring if information is available.

We expect to find most data from trials conducted in high-income countries. If this is the case, the results may need to be extrapolated to different healthcare settings, which would reduce the external validity of our review. Consequently, the actual beneficial and harmful effects observed in everyday clinical practice may differ significantly from those reported in the trials and, therefore, in our review.

Another limitation is the lack of detailed cost-effectiveness analyses, which is beyond the scope of this review. Instead, our review is on the clinical/patient-important effects of the different types of insulin. However, we plan to gather data on the costs of the interventions. If the clinical outcomes are similar between the two groups, cost may ultimately influence the choice of intervention, particularly in middle- or low-income countries. However, if one intervention is superior based on clinical outcomes, the cost of the intervention must be evaluated alongside the costs of any clinical complications.

The results of our review may also be affected by publication bias. Publication bias (i.e., when studies with positive or significant results are more likely to be published than those with negative or inconclusive findings) may skew our findings toward favorable outcomes. Similarly, industry funding for trials may lead to selective reporting of favorable outcomes that support the company's product. Thus, we risk overestimating the beneficial effects and underestimating the harmful effects of rapid-acting insulin analogues. We will include data from both published trials, unpublished trials, and clinical study reports and thereby reduce the risk of publication bias. We also plan to incorporate publication bias into our GRADE assessment of the results.

Missing data in the included trials may also affect our findings. Depending on the cause, missing data can reduce statistical power and lead to bias, ultimately resulting in incorrect conclusions. We plan to contact all trial authors to obtain any relevant missing data. We will also conduct sensitivity analyses (best–worst and worst-best scenarios) to evaluate the potential effects of missing data on primary and secondary outcomes. However, if the extent of missing data remains unclear, these analyses may not be feasible. Missing data will also be included in our risk of bias assessments.

Lastly, we have decided to only include randomized clinical trials. By excluding cluster-randomized trials, quasi-randomized trials, and observational studies, there is a risk of overlooking rare and late-occurring adverse events. It may be relevant to assess rare and late-occurring adverse effects of regular human insulins and rapid-acting insulin analogues in cluster-randomized trials, quasi-randomized trials, or observational studies. However, the significant risk of confounding by indication, which may skew results from non-randomized studies, limits the clinical relevance of incorporating such findings. Hopefully, future trials in this field involve large sample sizes to adequately evaluate relatively rare events and incorporate long-term follow-up assessments.

Abbreviations

GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HbA1c	Glycosylated hemoglobin A1c
FDA	US Food and Drug Administration
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
ICH-GCP	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice
CENTRAL	Cochrane Central Register of Controlled Trials
MEDLINE	Medical Literature Analysis and Retrieval System Online
EMBASE	Excerpta Medica database
LI-LACS	Latin American and Caribbean Health Sciences Literature
SCI-EXPANDED	Science Citation Index Expanded
CPCI-S	Conference Proceedings Citation Index—Science
HTA	Health Technology Assessment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB 2	Cochrane Risk of Bias tool—version 2
RR	Risk ratios
CI	Confidence interval
MD	Mean difference
SMD	Standardized mean difference
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02729-4.

Supplementary Material 1.

Supplementary Material 2.

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All authors approve publication of the protocol.

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