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Primary Outcomes Reporting in Trials in Pediatric Diabetes Mellitus: A Systematic Review

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Abstract

Objective: Our objective was to systematically review randomized clinical trials (RCTs) in pediatric diabetes mellitus (DM) to assess reporting of (i)primary outcome, (ii)outcome measurement properties, and (iii)adverse events.

Methods: Electronic searches in MEDLINE, EMBASE, CINAHL, Cochrane SR, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were undertaken. The search period was between 2001 and 2014. English-language RCTs on children younger than 21 with type I and type II DM were selected. We excluded studies of diagnostic or screening tools, multiple phase studies, protocols, and follow-up or secondary analysis of data.

Results: Of 11534 unique references, 208 type I and five type II diabetes RCTs were included. Of total 208 type I DM, 115 (55%) trials failed to report their primary outcome. Of 93 (45%) studies that reported primary outcome, 74 (80%) reported one and 19 (20%) more than one primary outcomes. Included trials measured 17 unique primary outcomes. Of 74 studies with single primary outcomes, 64 (86%) used biological/physiological measurements and 10 (14%) used instruments to measure their primary outcome; of these, eight (80%) provided measurement properties or related citation. Of the 208included studies on type I DM, 90 (43%) reported that adverse events occurred, 34 (16%) reported that no adverse events were identified, and 84 (41%) did not report on the presence or absence of adverse events. Four out of five type II DM trials included clearly stated their primary outcome and all reported no harmful effects associated with the intervention.

Conclusion: Despite tremendous efforts to improve reporting of clinical trials, clear reporting of primary outcomes of RCTs for pediatric DM is lacking. Adverse events due to DM interventions were often not reported in the included trials. Transparent reporting of primary outcome, validity of measurement tools, and adverse events need to be improved in pediatric DM trials.

Strengths and limitations of this study

- This is the first systematic review which evaluates condition of primary outcome reporting among RCTs of pediatric diabetes mellitus in an era post CONSORT.
- This study shows reporting of primary outcomes in RCTs conducted on diabetic children is not adequate.
- Reporting of adverse events and measurement properties of outcome measures also need to be improved.
- Knowledge synthesis efforts will be facilitated if heterogeneity in primary outcome selection is reduced.
- This review was restricted to English language, potentially, limiting generalizability of the findings to English literature.

INTRODUCTION

Randomized controlled trials (RCTs) are considered the gold standard to assess efficacy of interventions.[1] To ensure validity of findings in a clinical trial, it is paramount to report a clear set of outcomes, especially the primary outcomes measured, along with measurement tools used, and any assessment of adverse events. Health care professionals, patients, health policy developers and governments expect transparent reporting in trials to make sure the process of decision making is well informed and less biased.[2-4]

The *CONsolidated Standards Of Reporting Trials* (CONSORT) statement, which was initially introduced in 1996 to address the problem of incomplete reporting in the published clinical trials, has been updated twice since, in 2001 and 2010.[5, 6] Clear reporting of a study's primary outcome is essential, as it is used to inform the sample size calculation and is the main driver behind the trial's purpose. If primary outcomes are not reported clearly, the results of the trial may be jeopardized. While 585 journals have endorsed CONSORT since 1996, review studies have shown that primary outcomes were explicitly defined in only 45% and 53% of trial reports that were indexed in PubMed in 2000 and in 2006, respectively.[7, 8] Inadequate primary outcome reporting in pediatric trials has also been reported in some previous studies.[9, 10] To better understand the extent of the problem across fields, we have initiated a series of systematic reviews to assess primary outcomes reporting in trials (PORTal). Our first *PORTal* systematic review highlighted this problem in randomly sampled pediatric RCTs and demonstrated that 27.2% of studies published in high impact journals did not specify their primary outcomes.[11]

Pediatric diabetes mellitus (DM) is an emerging public health concern in the 21st century [12] and appropriate outcome reporting in DM trials is of great importance due to its high prevalence and economic burden worldwide.[13, 14] Reliable assessment of interventions on pediatric DM requires RCTs to be clearly reported.

In addition to clarity in defining primary outcomes, RCTs ought to demonstrate how they measured their primary outcome and whether their measurement tools were valid and reliable.[2, 14] Type and frequency of adverse events occurrence are also important to be studied and reported by RCTs in order to evaluate both the effectiveness of an intervention as well as possible harms associated with it.[5]

Primary objectives of this review were to assess RCTs of pediatric DM, published between 2001 and 2014 to evaluate reporting of: (i) primary outcome, (ii) measurement properties of primary outcome measure, and (iii) presence/absence of adverse events.

METHODS

A systematic review protocol has been published at the PROSPERO website (CRD42013005224) (see appendix 1). We followed PRISMA guideline for conducting this systematic review.[15]

Search Strategy

Electronic searches in MEDLINE, EMBASE, CINAHL, Cochrane SR, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were undertaken. Searches were limited to RCT study design, children under 21 years of age, English language, and dated since 2001 (last update Dec 2014).A five-year interval (1996-2001) since the initial publication of CONSORT was applied to our search to allow guideline implementation. The complete search strategy is available upon request to the corresponding author (see appendix 2 for Medline search strategy).

Study Selection

RCTs were selected if they were parallel, cross-over, factorial, and N-of-1 trials studying type I or type II DM, and examined any medical and non-medical interventions. Studies were excluded if the population included both children and adults, and if they were diagnostic studies, part of multi-phase trials, protocols, follow-up, and secondary analysis of data. Title and abstracts were screened for relevant entries and then full texts of potential articles were reviewed using pre-specified criteria for inclusion or exclusion. Four independent reviewers (SKA, MK, HCY, MZIH) performed study selection and discrepancies were resolved by consensus; for disagreements, a senior reviewer was sought (SV).

Data Extraction

Using a standardized form, four independent reviewers performed data extraction (SKA, HCY) and verification (MK, MZIH).Collected data included journal name, publication year, design of

the study, age, sex, sample size, disease condition, intervention and comparator(s)of interest, primary outcome(s), outcome measures, measurement tools and their properties, and adverse events. For more investigation documented journal impact factors (IF) were obtained for the year 2014 (InCites Journal Citation Reports; https://jcr.incites.thomsonreuters.com).

Full text articles were searched for any explicit indication of primary outcome. A variety of terms for the concept of 'outcome' were accepted including 'endpoint', 'variable', 'outcome variable', 'objective', 'pre-specified outcome', 'dependent variable', 'efficacy parameter', or equivalents. After identifying the primary outcome, if it was not a biological/physiological measure (e.g., blood tests), we sought for its measurement tool and reporting of measurement properties (validity and reliability), in addition to any relevant citation(s). Furthermore, any assessment of presence or absence of adverse events (and other relevant terms) was documented. If a study did not report at all on adverse events (its presence or absence), we classified that as "failed to report adverse eventsof intervention".

Data Analysis

Using descriptive analysis we presented percentages, mean, median, range, and inter quartile range (IQR) for the primary outcome and adverse events. Since this systematic review focused on reporting status of primary outcome and adverse events in published RCTs and was not intended to evaluate the effectiveness or efficacy of the interventions, the risk of bias and meta-analysis were not part of our study. Considering journals' impact factor (IF) for each published RCT, we grouped them into three batches using first quartile (Q1), interquartile range (Q3-Q1), and third quartile (Q3) of all IFs; journals with no available IF were coded as unknown. Statistical tests were performed for finding the differences between proportions of reporting primary outcome and adverse events among low, medium, and high impact factor journals using Stata statistical software release 14.

Patient involvement

Patients were not involved in the design and conduct of this study as the present study was a systematic review of published RCTs.

RESULTS

Our electronic search yielded 11534 unique references; full texts of 932 potentially relevant studies were retrieved for inclusion/exclusion. Four hundred and seventy seven out of 685 type I DM articles and 242 out of 247 type II DM references were excluded; reasons for exclusion are presented in PRISMA flow diagram (Figure 1). Finally, 208 RCTs of type I and 5 RCTs of type II pediatric DM were included for this systematic review.

Diabetes mellitus type I

Of 208 RCTs, 160 (77%) had parallel and 48 (33%) had crossover groups design. Total population was 18,676 and sample sizes ranged from 7 to 689 participants (Median: 50, IQR: 30-111). Other general characteristics of the studies are summarized in Table 1. Interventions comprised different forms of insulin therapy, oral medications, dietary, educational, and other medical interventions for glucose monitoring and insulin delivery methods.

Table 1. General characteristics of the included studies

RCTs' Characteristics		**Diabetes type I RCTs (n=208)**	**Diabetes type II RCTs (n=5)**
Journals' impact factor	High (≥8.42) Medium (≥2.57 and <8.42) Low (<2.57) Unknown	53 (25.5) 59 (28.4) 79 (38) 17 (8.2)	3 (60) 2 (40) 0 (0) 0 (0)
Age range	Range of actual age (years) Range of mean (years)	1-21 2.9-17.7	8-18 13.6-15
Design type	Parallel Crossover	160 (77) 48 (23)	4 (80) 1 (20)
Sample size	Range Mean (SD) Median (IQR)	7-689 Mean: 90 (101.9) Median: 50 (30-111)	13-699 Mean: 245 (272.9) Median: 146 (82-285)
Type of Intervention	Insulin/drug-based Diet-based Education-based Other Medical intervention Others	81 (38.9) 20 (9.6) 39 (18.8) 11 (5.3) 57 (27.4)	4 (80) 0 (0) 0 (0) 1 (20) 0 (0)

Controls	Placebo Usual care/No treatment/Waitlist Other treatment	25 (12) 83 (39.9) 100 (48.1)	2 (40) 0 (0) 3 (60)

* Data are presented as n (%)

Primary Outcomes

Of 208 RCTs, 93 (45%) studies clearly reported their primary outcome while115 (55%) did not. Of the 93 studies that clearly reported a primary outcome, 74 (80%) reported one primary outcome, 13 (14%) reported two primary outcomes, and 6 (6%) identified between three to seven primary outcomes. Among these outcomes (n=93), 87 (93.5%) were biological/physiological, and the rest were non-physiological (Table 2).Overall, included trials used 17 uniquely different primary outcomes. Forty five (48.4%) of these primary outcomes measured hemoglobin-A1C and 26 (28%) of them measured blood glucose levels.

Table 2: Frequency & type of primary outcomes in clinical trials of type I diabetes mellitus

Outcome categories	**Primary outcomes**	**Frequency* n (%)**
Physiological measures	HbA1C levels	45 (48.4)
	Blood glucose levels	26 (28)
	C-peptide levels	6 (6.4)
	Insulin sensitivity	1 (1.07)
	Carbohydrate counting accuracy	1 (1.07)
	Fructosamine levels	1 (1.07)
	Drug concentration levels	2 (2.1)
	Endothelial function	2 (2.1)
	Thyroid Gland volume	1 (1.07)
	Change in creatinine clearance rate	1 (1.07)
	Epinephrine response to hypoglycemia	1 (1.07)
Non physiological measures	Treatment Fidelity	1 (1.07)
	Perceived diabetes self-efficacy	1 (1.07)
	Preference for NovoTwist versus screw-thread needles in children and adolescents	1 (1.07)
	Health-related quality of life	1 (1.07)
	Macro and micronutrient composition of different diets	1 (1.07)
	Daily step count (exercise measurements)	1 (1.07)

* Some studies used more than one primary outcome

Outcome Measures

Of 74 studies that reported a single primary outcome, 64(86%) used biological/physiological measurements including measurements of glycemic control (e.g., hemoglobin-A1c (HbA1c), blood glucose) (Table 2).Ten (14%) trials used an outcome measurement instrument to measure their primary outcome. Of these, four provided both measurement properties and citation for the instrument used; three provided only the citation; one only measurement properties, and two provided neither.

Adverse Events

Of 208 studies, 90(43%) reported adverse event(s) associated with the intervention under study, 34 (16%) reported the absence of adverse events, and 84 (41%) failed to report on the presence/absence of adverse events.

Based on quartiles of journals IFs, three levels of low (IF<2.57), medium (2.57≥IF< 8.42), and high (IF≥8.42) were established. There was no statistically significant difference among studies published in low, medium and high IF journals in terms of primary outcome reporting (P=0.5) and likewise no significant differences in reporting adverse events (P=0.2) (Table 3).

With regard to date of publication, an upward trend was observed in reporting primary outcome(s) over time (Figure 2).However, endorsing CONSORT guideline did not influence the reporting of primary outcomes. Of 208 included trials 98 (47%) were published in CONSORT-endorsing journals. Among those, 49 (50%) reported their primary outcome, while 44 (40%) of 110 trials published in non-endorsing CONSORT journals reported a primary outcome (P=0.1).[16]

Table 3: Frequency distribution of primary outcome and adverse event reporting by journals impact factors

Impact factor		Low (n=46)*	Medium (n=92)	High (n=53)	Chi^2 test
Primary outcome	Reported	16 (34.8)**	41 (44.6)	21 (39.6)	p-value=0.5
	Failed to report	30 (65.2)	51 (55.4)	32 (60.4)	
Adverse events	Reported	22 (47.8)	31 (33.7)	19 (35.8)	p-value=0.2
	Failed to report	24 (52.2)	61 (66.3)	34 (64.2)	

* Low Impact Factor (<2.57), medium IF (2.57≥IF< 8.42), and high IF (≥8.42); **All data are presented as n (%)

Diabetes mellitus type II

General characteristics of the five included studies have been described in Table 1. Four studies (80%) clearly identified a single primary outcome. All of the outcomes were related to glycemic control of diabetes; all used physiological measurements. All studies reported on harmful effect of interventions.

DISCUSSION

This is the first study to present a comprehensive overview of primary outcome and adverse events reporting among published RCTs in pediatric DM.As RCTs are recognized for their importance in medical research, methodological examinations of their reports is crucial for appropriate medical practice.[17]

It has been 20 years since the initial CONSORT statement recommended guidelines for minimal necessary RCT reporting. Since then, reporting of study rationale, objective, recruitment methods, sample size calculation, allocation concealment, and method of sequence generation have been improving among published clinical trials.[18] Nevertheless, we and other groups have shown that reporting of primary outcome, measurement tools and reporting of the validity and reliability of those tools have not been improved alike.[7, 19-21] A systematic review performed on a random sample of pediatric RCTs published in high-impact CONSORT-endorsing journals reported that 27.2% of the trials failed to report any primary outcome.[10] In our analysis, we demonstrated suboptimal reporting of primary outcomes and adverse events of interventions in journals with high and low impact factor, regardless of whether they endorsed the CONSORT guideline or not.

DM lends itself to use of biological/physiological measurements. Accuracy in measurement of these biological or physiological assessments is outside our scope, but we are reassured that the other instruments used (e.g. surveys) had appropriate citations regarding their measurement properties (reliability, validity). Furthermore, we found heterogeneity in primary outcomes used in our included studies (only half of them used similar primary outcomes). According to the COMET (Core Outcome Measures in Effectiveness Trials) initiative,[22] consistency in primary outcome measurement between trials is necessary to allow for meaningful knowledge synthesis. Most systematic reviews try to assess treatment effectiveness by compiling evidence from multiple RCTs; however, these efforts are hampered by heterogeneity in outcome measurement.

Strengths and limitations:

To our knowledge, this systematic review is unique in that it has evaluated condition of primary outcome reporting among RCTs of pediatric DM in an era post CONSORT. A robust and systematic methodology was employed including independent and duplicate screening/data extraction using pre-specified criteria and data extraction form. This review was a complement to our previous work that examined only a random sample of all pediatric RCTs published in high profile peer-reviewed journals.[11] We further examined primary outcome and adverse event reporting on the basis of high, medium, and low impact factor journals.

As a possible limitation, this review was restricted to English language, potentially, limiting generalizability of the findings to English literature.

Implications:

The results of this systematic review underscore the potential opportunities for improving quality of reporting in clinical trials. It is important for journals that endorse CONSORT to ensure that authors and reviewers use the checklist to confirm reporting is consistently complete and transparent. Pediatric DM is an important condition with increasing prevalence, and will have global impact on health. To be of most use to clinicians and policy-makers, trials in this field would benefit from improved reporting of primary outcomes and adverse events. In addition, development of a core outcome set (to reduce heterogeneity in primary outcome measurements) and using outcome measurement instruments that are valid and reliable and reported as such are

of great importance to support quality meta-analysis leading to more precise and unbiased findings.

Figure 1: PRISMA flow diagram of study selection

Figure 2: Proportion of studies that reported primary outcome(s) by year of publication

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Competing interests

I/We have read and understood the BMJ Group policy on declaration of interests and declare the following interests:

Grant funding for research but no other competing interest

"Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: this study has had financial support from the Canadian Institutes of Health Research (CIHR) for the submitted work; the authors declare they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Authors' contribution:

Each of the authors met the criteria for authorship established by the ICMJE. Each author contributed substantial to 1) conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Samaneh Khanpour Ardestani/SKA: Dr. Khanpour Ardestani was substantially involved in design and conduct of the study, screening articles, extracting the data, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Mohammad Karkhaneh/MK: Dr. Karkhaneh was substantially involved in conduct of the study, screening articles, extracting the data, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Hai Chuan Yu/HCY: Mr. Yu was substantially involved in screening articles, extracting the data, revising the manuscript and final approval of the version to be published.

Muhammad Iqbal Zafar Hydrie/MIZH: Dr. Hydrie was substantially involved in screening the articles, extracting the data, revising the manuscript and final approval of the version to be published.

Sunita Vohra/SV (corresponding author): Dr. Vohra was substantially involved in design and conduct of the study, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Transparency declaration:

"The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

Data sharing statement

The complete search strategy is available upon request to the corresponding author.

Ethical approval:

Ethical approval was not required for this study.

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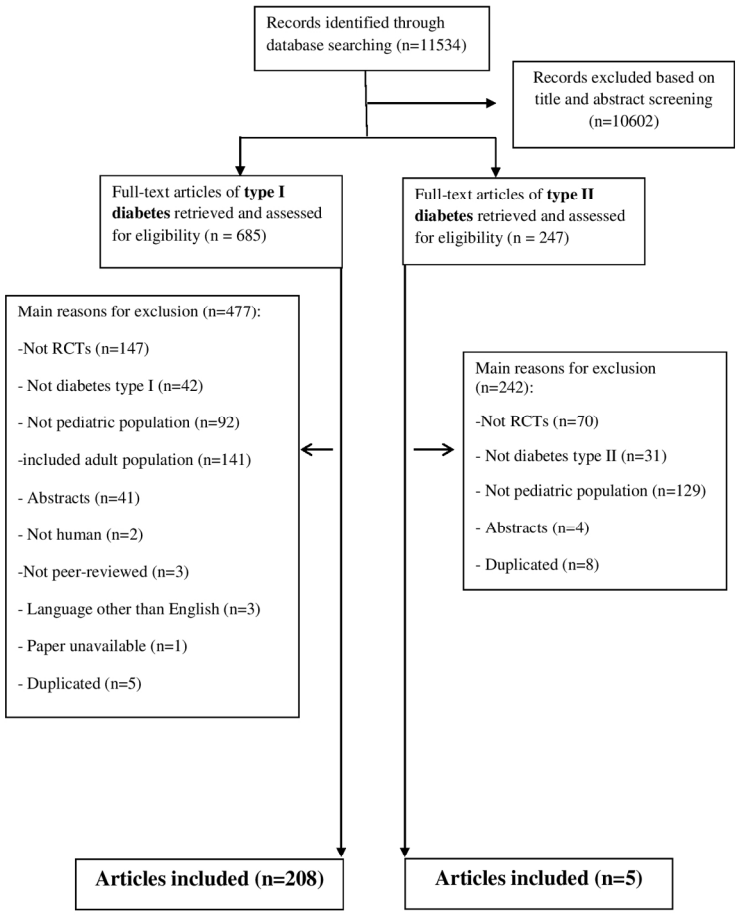

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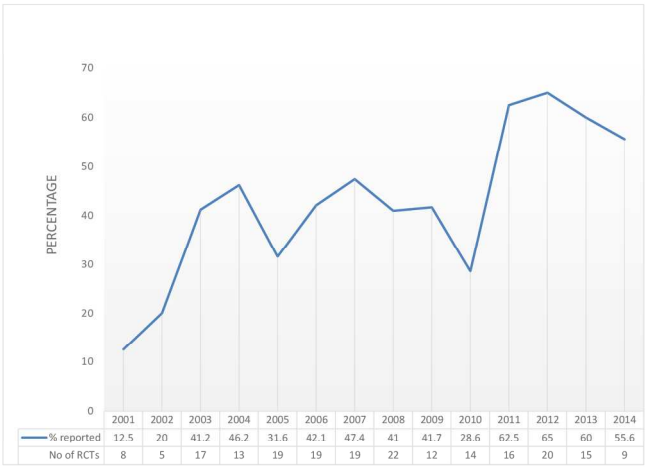

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
% reported	12.5	20	41.2	46.2	31.6	42.1	47.4	41	41.7	28.6	62.5	65	60	55.6
No of RCTs	8	5	17	13	19	19	19	22	12	14	16	20	15	9

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Alberta Innovates Health Solutions; Canadian Institute for Health Research

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Dr	Susanne	King-Jones	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada
Dr	Liliane	Zorzela	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
How well were the primary outcomes identified and reported in pediatric diabetes randomized controlled trials?

What were the psychometric properties of the instruments used to measure outcomes in these trials?

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
The following electronic bibliographic databases are included in the search: MEDLINE, EMBASE, CINAHL, The Cochrane Library, Cochrane SR, and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms were related to diabetes (e.g. diabetes mellitus, juvenile onset). The terms were combined with the MEDLINE filter for randomized controlled clinical trials and pediatrics (under 21 years old). The search terms will be adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where these are

available. The search will be limited to English-language studies. Studies published between January 2001 and May 2012 will be considered.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Diabetes mellitus type 1 results when the pancreas no longer produces significant amounts of the hormone insulin, owing to the destruction of the insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Type 1 diabetes is treated with insulin replacement therapy—either via subcutaneous injection or insulin pump. Treatment of diabetes focuses on lowering blood sugar or glucose (BG) to the near normal range, approximately 80–140 mg/dl (4.4–7.8 mmol/L). Diabetes mellitus type 2 is an intricate metabolic disorder with heterogeneous etiologies and is increasing in prevalence. Social, behavioral and environmental risk factors can trigger the disease in genetically susceptible people. Insulin resistance and insulin secretory failure are the main mechanisms involved in its pathophysiology. Lifestyle modification (nutritional and exercise) beside pharmacological therapy, such as insulin and oral antihyperglycemic medications (e.g metformin) are key management approaches.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Pediatric patients 0-20 years of age.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

We will include any RCTs looking at interventions aimed at managing diabetes (e.g. different insulin regimens, educational therapies, etc). We will exclude diabetes prevention trials as well as trials assessing diabetes diagnostic tools. We will also exclude pilot studies, secondary studies, and studies validating psychometric properties of measurement tools.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Any comparator will be allowed, including placebo and usual care.

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Randomized controlled trials (RCTs) will be included; we will exclude pilot studies, multi-stage trials, trials of diagnostic tools, and secondary reports/follow up studies.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Any setting dealing with pediatric health care will be included.

24 Primary outcome(s)

Give the most important outcomes.

This study aims to assess the quality of reporting, heterogeneity in selecting and validity of outcome measures presented by authors of pediatric diabetes trials. This study will not restrict the outcomes being assessed as the goal is to identify current trends in pediatric diabetes research reporting. Some examples of the outcomes often assessed include glycemic control, as measured by HbA1c levels, as well as insulin doses and hypoglycemic episodes.

Give information on timing and effect measures, as appropriate.

We will not include an assessment of effect or timing.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
None.

Give information on timing and effect measures, as appropriate.
None.

26 Data extraction (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Duplicate articles will be removed prior to review. Two reviewers will then individually screen article titles and abstracts for inclusion. Full text of potentially included articles will be obtained and assessed for inclusion using preset criteria. Data will be extracted by one reviewer and verified by a second reviewer. Where disagreement between reviewers exists, the reviewers will attempt to reach consensus through discussion and a third reviewer will be consulted where necessary. Data to be extracted include: age and gender of participants, study design, condition, interventions and controls under study, details of outcomes and outcome measurement tools, and details of safety/harms assessment.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Because we are focusing on outcome reporting, risk of bias will not be assessed.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
For the purpose of this systematic review data combining may not be feasible. If appropriate, count data will be presented using proportions and will be analyzed using descriptive statistics and Chi-squared tests.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned.

Review general information

30 Type and method of review
Select the type of review and the review method from the drop down list.
Intervention, Systematic review, Other

Methodologic

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Canada

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
We plan to submit a paper to a peer reviewed journal relevant to pediatric diabetic medicine.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
diabetes type 1 or type 2

reporting

outcomes

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Medline search strategy:

1. randomized controlled trial/

2. clinical trial.pt.

3. randomi?ed.ti,ab.

4. placebo.ti,ab.

5. dt.fs.

6. randomly.ti,ab.

7. trial.ti,ab.

8. groups.ti,ab.

9. or/1-8

10. Animals/

11. Humans/

12. 10 not (10 and 11)

13. 9 not 12

14. exp Diabetes Mellitus/

15. exp Diabetes Mellitus, Type 2/

16. exp Diabetes Mellitus, Type 1/

17. type 1 diabetes.mp.

18. type 2 diabetes.mp.

19. diabet*.mp.

20. diabet* syndrome*.mp.

21. childhood-onset diabetes.mp.

22. Juvenile onset diabetes.mp.

23. (juvenile adj2 diabet*).mp.

24. Insulin dependent diabet*.mp.

25. juvenile diabetes.mp.

26. IDDM.mp.

27. or/14-26

28. 13 and 27

29. limit 28 to "all child (0 to 18 years)"

30. limit 29 to english language

31. limit 30 to yr="2001 - 2014"

BMJ Open

Primary Outcomes Reporting in Trials of Pediatric Type 1 Diabetes Mellitus: A Systematic Review

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Primary Outcomes Reporting in Trials of Pediatric Type 1 Diabetes Mellitus: A Systematic Review

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Abstract

Objective: Our objective was to systematically review randomized clinical trials (RCTs) of pediatric type 1 diabetes mellitus (T1 DM) to assess reporting of (i) primary outcome, (ii) outcome measurement properties, and (iii) presence or absence of adverse events.

Methods: Electronic searches in MEDLINE, EMBASE, CINAHL, Cochrane SR, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were undertaken. The search period was between 2001 and 2017. English-language RCTs on children younger than 21 with T1 DM were selected. We excluded studies of diagnostic or screening tools, multiple phase studies, protocols, and follow-up or secondary analysis of data.

Results: Of 11816 unique references, 231 T1 DM RCTs were included. Of total 231 included studies, 117 (50.65%) trials failed to report their primary outcome. Of 114 (49.35%) studies that reported primary outcome, 88 (77.2%) reported one and 12 (22.8%) more than one primary outcomes. Of 114 studies that clearly stated their primary outcome, 101 (88.6%) used biological/physiological measurements and 13 (11.4%) used instruments (e.g. questionnaires, scales, etc.) to measure their primary outcome; of these, 12 (92.3%) provided measurement properties or related citation. Of the 231 included studies, 105 (45.5%) reported that adverse events occurred, 39 (16.9%) reported that no adverse events were identified, and 87 (37.7%) did not report on the presence or absence of adverse events.

Conclusion: Despite tremendous efforts to improve reporting of clinical trials, clear reporting of primary outcomes of RCTs for pediatric T1 DM is still lacking. Adverse events due to DM interventions were often not reported in the included trials. Transparent reporting of primary outcome, validity of measurement tools, and adverse events need to be improved in pediatric T1 DM trials.

Strengths and limitations of this study

- This is the first systematic review which evaluates the condition of primary outcome reporting among RCTs of pediatric type 1 diabetes mellitus in an era post CONSORT.
- This study shows reporting of primary outcomes in RCTs conducted on diabetic children is not adequate.
- Reporting of adverse events and measurement properties of outcome measures also need to be improved.
- Knowledge synthesis efforts will be facilitated if heterogeneity in primary outcome selection is reduced.
- This review was restricted to English language, potentially, limiting generalizability of the findings to English literature.

INTRODUCTION

Randomized controlled trials (RCTs) are considered the gold standard to assess efficacy of interventions.(1) To ensure validity of findings in a clinical trial, it is paramount to report a clear set of outcomes, especially the primary outcomes measured, along with measurement tools used, and any assessment of adverse events. Health care professionals, patients, health policy developers and governments expect transparent reporting in trials to make sure the process of decision making is well informed and less biased.(2-4)

The *CONsolidated Standards Of Reporting Trials* (CONSORT) statement, which was initially introduced in 1996 to address the problem of incomplete reporting in the published clinical trials, has been updated twice since, in 2001 and 2010.(5, 6) Clear reporting of a study's primary outcome is essential, as it is used to inform the sample size calculation and is the main driver behind the trial's purpose. If primary outcomes are not reported clearly, the results of the trial may be jeopardized. While 585 journals have endorsed CONSORT since 1996, review studies have shown that primary outcomes were explicitly defined in only 45% and 53% of trial reports that were indexed in PubMed in 2000 and in 2006, respectively.(7, 8) Inadequate primary outcome reporting in pediatric trials has also been reported in some previous studies.(9, 10) To better understand the extent of the problem across fields, we have initiated a series of systematic reviews to assess primary outcomes reporting in trials (PORTal). Our first *PORTal* systematic review highlighted this problem in randomly sampled pediatric RCTs and demonstrated that 27.2% of studies published in high impact journals did not specify their primary outcomes. (11)

Pediatric diabetes mellitus (DM) is an emerging public health concern in the 21st century (12) and appropriate outcome reporting in DM trials is of great importance due to its high prevalence and economic burden worldwide.(13, 14) Reliable assessment of interventions on pediatric DM requires RCTs to be clearly reported.

In addition to clarity in defining primary outcomes, RCTs ought to demonstrate how they measured their primary outcome and whether their measurement tools were valid and reliable.(2, 14)Type and frequency of adverse events occurrence are also important to be studied and reported by RCTs in order to evaluate both the effectiveness of an intervention as well as possible harms associated with it.(5)

Primary objectives of this review were to assess RCTs of pediatric DM, published between 2001 and 2017 to evaluate reporting of (i) primary outcome, (ii) measurement properties of primary outcome measure, and (iii) presence/absence of adverse events.

METHODS

A systematic review protocol has been published at the PROSPERO website (CRD42013005224) (see appendix 1). We followed PRISMA guideline for conducting this systematic review. (15)

Search Strategy

Electronic searches in MEDLINE, EMBASE, CINAHL, Cochrane SR, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were undertaken. Searches were limited to RCT study design, children under 21 years of age, English language, and dated since 2001 (last update Jan 2017). A five-year interval (1996-2001) since the initial publication of CONSORT was applied to our search to allow guideline implementation. The complete search strategy is available upon request to the corresponding author (see appendix 2 for Medline search strategy).

Study Selection

RCTs were selected if they were parallel, cross-over, factorial, and N-of-1 trials studying type 1, and examined any medical and non-medical interventions. Studies were excluded if the population included both children and adults, and if they were diagnostic studies, part of multi-phase trials, protocols, follow-up, and secondary analysis of data. Title and abstracts were screened for relevant entries and then full texts of potential articles were reviewed using pre-specified criteria for inclusion or exclusion. Four independent reviewers (SKA, MK, HCY, MZIH) performed study selection and discrepancies were resolved by consensus; for disagreements, a senior reviewer was sought (SV).

Data Extraction

Using a standardized form, four independent reviewers performed data extraction (SKA, HCY) and verification (MK, MZIH). Collected data included journal name, publication year, design of

the study, age, sex, sample size, disease condition, intervention and comparator(s)of interest, primary outcome(s), outcome measures, measurement tools and their properties, and adverse events. For more investigation, documented journal impact factors (IF) were obtained for the year 2015 (InCites Journal Citation Reports; https://jcr.incites.thomsonreuters.com).

Full text articles were searched for any explicit indication of primary outcome. A variety of terms for the concept of 'outcome' were accepted including 'endpoint', 'variable', 'outcome variable', 'objective', 'pre-specified outcome', 'dependent variable', 'efficacy parameter', or equivalents. If studies clearly stated their primary outcome using the mentioned terminology or described with a synonymous term anywhere in their manuscript, they were considered as "reported primary outcome". We also considered them as "reported", if they explicitly stated the outcome used for the sample size calculation. If studies provided several outcomes without specifying their primary, we considered them as "failed to report primary outcome". After identifying the primary outcome, if it was not a biological/physiological measure (e.g., blood tests), we sought for its measurement tool and reporting of measurement properties (validity and reliability), in addition to any relevant citation(s). Furthermore, any assessment of presence or absence of adverse events (and other relevant terms) was documented. If a study did not report at all on adverse events (its presence or absence), we classified that as "failed to report adverse events of intervention".

Data Analysis

Using descriptive analysis, we presented percentages, mean, median, range, and inter quartile range (IQR) for the primary outcome and adverse events. Since this systematic review focused on reporting status of primary outcome and adverse events in published RCTs and was not intended to evaluate the effectiveness or efficacy of the interventions, the risk of bias and meta-analysis were not part of our study. Considering journals' impact factor (IF) for each published RCT, we grouped them into three batches using first quartile (Q1), interquartile range (Q3-Q1), and last quartile (Q4) of all IFs; journals with no available IF were coded as unknown. Chi-square test was performed for finding the differences between proportions of reporting primary outcome and adverse events among low, medium, and high impact factor journals using Stata statistical software release 14. (16)

Patient involvement

Patients were not involved in the design and conduct of this study as the present study was a systematic review of published RCTs.

RESULTS

Our electronic search yielded 11816 unique references; full texts of 986 potentially relevant studies were retrieved for inclusion/exclusion. Seven hundred and fifty-five out of 986 retrieved articles were excluded; reasons for exclusion are presented in PRISMA flow diagram (Figure 1). Finally, 231 RCTs of pediatric T1 DM were included for this systematic review.

Type 1 Diabetes Mellitus

Of 231 RCTs, 177 (76.6%) had parallel and 54 (23.4%) had crossover groups design. Total population was 21,014 and sample sizes ranged from 7 to 689 participants (Median: 51.5, IQR: 30-110.75). Other general characteristics of the studies are summarized in Table 1. Interventions comprised different forms of insulin therapy, oral medications, dietary, educational, and other medical interventions for glucose monitoring and insulin delivery methods.

Table 1. General characteristics of the included studies

RCTs' Characteristics		Diabetes type 1 RCTs (n=231)
Journals' impact factor	High (≥8.42) Medium (≥2.57 and <8.42) Low (<2.57) Unknown	59 (25.5) 115 (49.8) 42 (18.2) 15 (6.5)
Age range	Range of actual age (years) Range of mean (years)	1-21 2.9-17.7
Type of design	Parallel Crossover	177 (76.6) 54 (23.4)
Sample size	Range Mean (SD) Median (IQR)	7-689 Mean: 91.37 (103.38) Median: 51.5 (30-110.75)

Type of Intervention	Insulin/drug-based Diet-based Education-based Other Medical intervention Others	91 (39.4) 21 (9.1) 41 (17.7) 17 (7.4) 61 (26.4)
Controls	Placebo Usual care/No treatment/Waitlist Other treatment	29 (12.5) 97 (42) 105 (45.5)

* Data are presented as n (%)

Primary Outcomes

Of 231 RCTs, 114 (49.4%) studies explicitly identified their primary outcome while 117 (50.6%) did not. Of the 114 studies that transparently reported a primary outcome, 88 (77.2%) reported one primary outcome, 18 (15.8%) reported two primary outcomes, and 8 (7%) identified between three to seven primary outcomes. Among studies with a single primary outcome (n=88), 83 (94.3%) were biological/physiological measurements, and the rest (n=5, 5.7%) were non-physiological (Table 2). Overall, these trials used 14 uniquely different primary outcomes. Out of 88 studies with single primary outcomes, forty eight (54.5%) measured hemoglobin-A1C and 24 (27.3%) measured blood glucose levels.

Table 2. Frequency & type of primary outcomes in clinical trials of type 1 diabetes mellitus

Outcome categories	**Primary outcomes**	**Frequency* n (%)**
Physiological measures	HbA1C levels	48 (54.5)
	Blood glucose levels	24 (27.3)
	C-peptide levels	4 (4.5)
	Endothelial function	2 (2.3)
	Time to metabolic normalization	1 (1.14)
	Fructosamine levels	1 (1.14)
	Insulin sensitivity	1 (1.14)
	Change in creatinine clearance rate	1 (1.14)
	Epinephrine response to hypoglycemia	1 (1.14)
Non physiological measures	Treatment Fidelity	1 (1.14)
	Perceived diabetes self-efficacy	1 (1.14)
	Preference for NovoTwist versus screw-thread needles in	1 (1.14)

	children and adolescents	
	Health-related quality of life	1 (1.14)
	Macro and micronutrient composition of different diets	1 (1.14)

* Some studies used more than one primary outcome

Outcome Measures

Of 114 studies that clearly defined their primary outcome, 101(88.6%) used biological/physiological measurements including measurements of glycemic control (e.g., hemoglobin-A1c (HbA1c), blood glucose). Thirteen (11.4%) trials used an outcome measurement instrument to measure their primary outcome. Of these 13, five provided both measurement properties and citation for the instruments used; seven provided only the citation and one provided neither.

Adverse Events

Of 231 studies, 105(45.5%) reported adverse event(s) associated with the intervention under study, 39 (16.9%) reported the absence of adverse events, and 87 (37.7%) failed to report on the presence/absence of adverse events.

Journals' impact factor and CONSORT endorsement

Based on quartiles of journals IFs, three levels of low (IF<2.57), medium (2.57≥IF< 8.42), and high (IF≥8.42) were established. There was no statistically significant difference among studies published in low, medium and high IF journals regarding adverse event reporting (P=0.7). However, failing to report primary outcome was associated with publishing in low IF journals (P=0.04) (Table 3).

Considering the date of publication, an upward trend was observed in reporting primary outcome(s) over time (Figure 2). However, endorsing CONSORT guideline did not influence the reporting of primary outcomes. Of 231 included trials, 108 (46.8%) were published in CONSORT-endorsing journals. Among those, 57 (52.8%) reported their primary outcome, while 57 (46.3%) of 123 trials published in non-endorsing CONSORT journals reported a primary outcome (P=0.3). (17)

Table 3. Frequency distribution of primary outcome and adverse event reporting by journals impact factors

Impact factor		Low (n=42)*	Medium (n=115)	High (n=59)	Chi^2 test
Primary outcome	Reported (n=114)	14 (12.3)**	64 (56.1)	31 (27.2)	p-value=0.04
	Failed to report (n=117)	28 (23.9)	51 (43.6)	28 (23.9)	
Adverse events	Reported (n=144)	25 (17.4)	76 (52.8)	39 (27.1)	p-value=0.7
	Failed to report (n=87)	17 (19.5)	39 (44.8)	20 (22.9)	

* Low Impact Factor (<2.57), medium IF (2.57≥IF< 8.42), and high IF (≥8.42); **All data are presented as n (%)

DISCUSSION

This is the first study to present a comprehensive overview of primary outcome and adverse events reporting among published RCTs in pediatric T1 DM.As RCTs are recognized for their importance in medical research, methodological examinations of their reports is crucial for appropriate medical practice.(18)

It has been 20 years since the initial CONSORT statement recommended guidelines for minimal necessary RCT reporting. Since then, reporting of study rationale, objective, recruitment methods, sample size calculation, allocation concealment, and method of sequence generation have been improving among published clinical trials.(19) Nevertheless, we and other groups have shown that reporting of primary outcome, measurement tools and reporting of the validity and reliability of those tools have not been improved alike.(7, 20-22) A systematic review performed on a random sample of pediatric RCTs published in high-impact CONSORT-endorsing journals reported that 27.2% of the trials failed to report any primary outcome.(10)In our analysis, we demonstrated suboptimal reporting of primary outcomes and adverse events of interventions in journals with high and low impact factor, regardless of whether they endorsed the CONSORT guideline or not. We were quite flexible regarding author terminology used to describe primary outcomes in articles. Given that, if authors did not explicitly specify their

primary outcome(s), we considered this issue as a failure in reporting. Failure in reporting primary outcome(s) may lead to selective outcome(s) reporting; (23)CONSORT and its extensions were intended to prevent biased reporting by ensuring primary outcomes are clearly and explicitly stated in all peer-reviewed published RCTs. This also influences the qualitative evaluation of RCTs in systematic reviews and meta-analyses using existing risk of bias tools.(24)Furthermore, heterogeneous outcomes challenge knowledge synthesis efforts to summarize data between trials and maximize its utility in decision-making.

DM lends itself to use of biological/physiological measurements. Accuracy in the measurement of these biological or physiological assessments is outside our scope, but we are reassured that the other instruments used (e.g. surveys) had appropriate citations regarding their measurement properties (reliability, validity). Furthermore, we found heterogeneity in primary outcomes used in our included studies (only half of them used similar primary outcomes). According to the COMET (Core Outcome Measures in Effectiveness Trials) initiative,(25)consistency in primary outcome measurement between trials is necessary to allow for meaningful knowledge synthesis. Most systematic reviews try to assess treatment effectiveness by compiling evidence from multiple RCTs; however, these efforts are hampered by heterogeneity in outcome measurement.

Strengths and limitations:

To our knowledge, this systematic review is unique in that it has evaluated the condition of primary outcome reporting among RCTs of pediatric T1 DM in an era post CONSORT. A robust and systematic methodology was employed including independent and duplicate screening/data extraction using pre-specified criteria and data extraction form. This review was a complement to our previous work that examined a random sample of all pediatric RCTs published in high profile peer-reviewed journals.(11) We further examined primary outcome and adverse event reporting on the basis of high, medium, and low impact factor journals.

As a possible limitation, this review was restricted to English language, potentially, limiting generalizability of the findings to English literature.

Implications:

The results of this systematic review underscore the potential opportunities for improving the quality of reporting in pediatric clinical trials. It is important for journals that endorse

CONSORT to ensure that authors and reviewers use the checklist to confirm reporting of main components of RCTs is complete and transparent. Pediatric DM is an important condition with increasing prevalence and will have global impact on health. To be of most use to clinicians and policy-makers, trials in this field would benefit from improved reporting of primary outcomes and adverse events. In addition, development of a core outcome set (to reduce heterogeneity in primary outcome measurements) and using outcome measurement instruments that are valid and reliable and reported as such are of great importance to support quality meta-analysis leading to more precise and unbiased findings.

Figure 1: Adapted version of PRISMA flow diagram of study selection

Figure 2: Proportion of studies that reported primary outcome(s) by year of publication

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Competing interests

I/We have read and understood the BMJ Group policy on declaration of interests and declare the following interests:

Grant funding for research but no other competing interest

"Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: this study has had financial support from the Canadian Institutes of Health Research (CIHR) for the submitted work; the authors declare they have no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Authors' contribution:

Each of the authors met the criteria for authorship established by the ICMJE. Each author contributed substantial to 1) conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Samaneh Khanpour Ardestani/SKA: Dr. Khanpour Ardestani was substantially involved in design and conduct of the study, screening articles, extracting the data, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Mohammad Karkhaneh/MK: Dr. Karkhaneh was substantially involved in the conduct of the study, screening articles, extracting the data, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Hai Chuan Yu/HCY: Mr. Yu was substantially involved in screening articles, extracting the data, revising the manuscript and final approval of the version to be published.

Muhammad Iqbal Zafar Hydrie/MIZH: Dr. Hydrie was substantially involved in screening the articles, extracting the data, revising the manuscript and final approval of the version to be published.

Sunita Vohra/SV (corresponding author): Dr. Vohra was substantially involved in design and conduct of the study, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Transparency declaration:

"The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

Data sharing statement

The complete search strategy is available upon request to the corresponding author.

Ethical approval:

Ethical approval was not required for this study.

Funding:

The study was supported by the Canadian Institutes of Health Research (CIHR). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the study.

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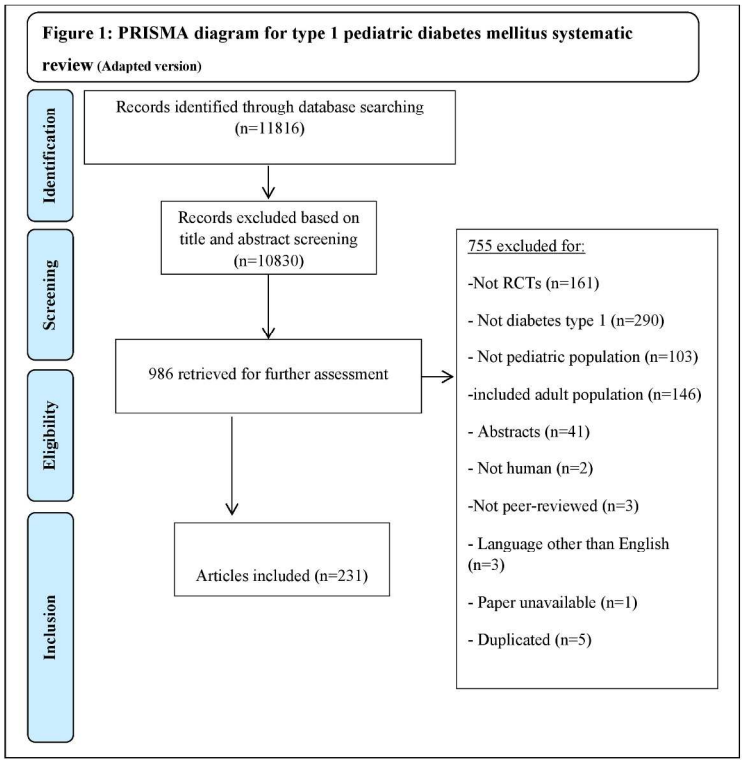

Figure 1: PRISMA diagram for type 1 pediatric diabetes mellitus systematic review (Adapted version)

215x279mm (300 x 300 DPI)

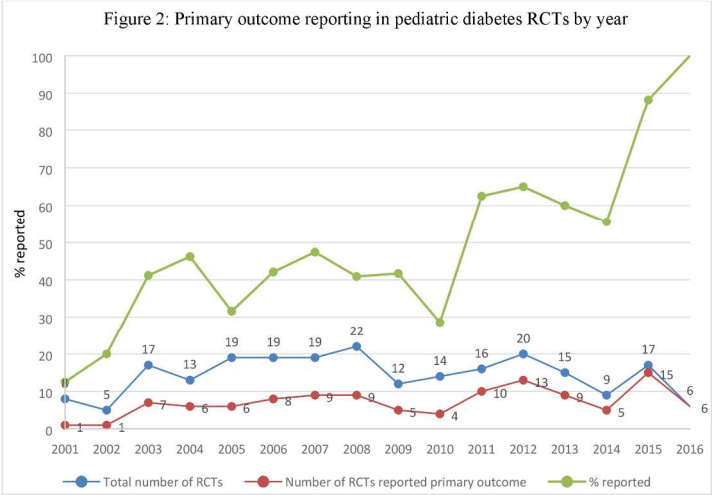

Figure 2: Primary outcome reporting in pediatric diabetes RCTs by year

215x279mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5,6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10,11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13-15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Systematic review of outcome measures in randomized controlled trails of pediatric diabetes management

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
01/05/2012

4 Anticipated completion date
Give the date by which the review is expected to be completed.
30/06/2016

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	No	Yes
Risk of bias (quality) assessment	No	Yes
Data analysis	No	Yes

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Sunita Vohra

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Department of Pediatrics, University of Alberta 1702 College Plaza 8215 - 112 Street NW Edmonton, AB Canada T6G 2C8

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
+1 780-492-6445

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Alberta Department of Pediatrics

Website address:
www.care.ualberta.ca

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Dr	Sunita	Vohra	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada
Dr	Muhammad Zafar	Hydrie	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada
Mr	Hai Chuan (Carlos)	Yu	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada
Dr	Samaneh	Khanpour Ardestani	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada
Dr	Mohammad	Karkhaneh	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Alberta Innovates Health Solutions; Canadian Institute for Health Research

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Dr	Susanne	King-Jones	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada
Dr	Liliane	Zorzela	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

How well were the primary outcomes identified and reported in pediatric diabetes randomized controlled trials?

What were the psychometric properties of the instruments used to measure outcomes in these trials?

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following electronic bibliographic databases are included in the search: MEDLINE, EMBASE, CINAHL, The Cochrane Library, Cochrane SR, and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms were related to diabetes (e.g. diabetes mellitus, juvenile onset). The terms were combined with the MEDLINE filter for randomized controlled clinical trials and pediatrics (under 21 years old). The search terms will be adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where these are

available. The search will be limited to English-language studies. Studies published between January 2001 and May 2012 will be considered.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Diabetes mellitus type 1 results when the pancreas no longer produces significant amounts of the hormone insulin, owing to the destruction of the insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Type 1 diabetes is treated with insulin replacement therapy—either via subcutaneous injection or insulin pump. Treatment of diabetes focuses on lowering blood sugar or glucose (BG) to the near normal range, approximately 80–140 mg/dl (4.4–7.8 mmol/L). Diabetes mellitus type 2 is an intricate metabolic disorder with heterogeneous etiologies and is increasing in prevalence. Social, behavioral and environmental risk factors can trigger the disease in genetically susceptible people. Insulin resistance and insulin secretory failure are the main mechanisms involved in its pathophysiology. Lifestyle modification (nutritional and exercise) beside pharmacological therapy, such as insulin and oral antihyperglycemic medications (e.g metformin) are key management approaches.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Pediatric patients 0-20 years of age.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

We will include any RCTs looking at interventions aimed at managing diabetes (e.g. different insulin regimens, educational therapies, etc). We will exclude diabetes prevention trials as well as trials assessing diabetes diagnostic tools. We will also exclude pilot studies, secondary studies, and studies validating psychometric properties of measurement tools.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Any comparator will be allowed, including placebo and usual care.

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Randomized controlled trials (RCTs) will be included; we will exclude pilot studies, multi-stage trials, trials of diagnostic tools, and secondary reports/follow up studies.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Any setting dealing with pediatric health care will be included.

24 Primary outcome(s)

Give the most important outcomes.

This study aims to assess the quality of reporting, heterogeneity in selecting and validity of outcome measures presented by authors of pediatric diabetes trials. This study will not restrict the outcomes being assessed as the goal is to identify current trends in pediatric diabetes research reporting. Some examples of the outcomes often assessed include glycemic control, as measured by HbA1c levels, as well as insulin doses and hypoglycemic episodes.

Give information on timing and effect measures, as appropriate.

We will not include an assessment of effect or timing.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
None.

Give information on timing and effect measures, as appropriate.
None.

26 Data extraction (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Duplicate articles will be removed prior to review. Two reviewers will then individually screen article titles and abstracts for inclusion. Full text of potentially included articles will be obtained and assessed for inclusion using preset criteria. Data will be extracted by one reviewer and verified by a second reviewer. Where disagreement between reviewers exists, the reviewers will attempt to reach consensus through discussion and a third reviewer will be consulted where necessary. Data to be extracted include: age and gender of participants, study design, condition, interventions and controls under study, details of outcomes and outcome measurement tools, and details of safety/harms assessment.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Because we are focusing on outcome reporting, risk of bias will not be assessed.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
For the purpose of this systematic review data combining may not be feasible. If appropriate, count data will be presented using proportions and will be analyzed using descriptive statistics and Chi-squared tests.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned.

Review general information

30 Type and method of review
Select the type of review and the review method from the drop down list.
Intervention, Systematic review, Other

Methodologic

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Canada

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
We plan to submit a paper to a peer reviewed journal relevant to pediatric diabetic medicine.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
diabetes type 1 or type 2

reporting

outcomes

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Medline search strategy:

1. randomized controlled trial/

2. clinical trial.pt.

3. randomi?ed.ti,ab.

4. placebo.ti,ab.

5. dt.fs.

6. randomly.ti,ab.

7. trial.ti,ab.

8. groups.ti,ab.

9. or/1-8

10. Animals/

11. Humans/

12. 10 not (10 and 11)

13. 9 not 12

14. exp Diabetes Mellitus/

15. exp Diabetes Mellitus, Type 2/

16. exp Diabetes Mellitus, Type 1/

17. type 1 diabetes.mp.

18. type 2 diabetes.mp.

19. diabet*.mp.

20. diabet* syndrome*.mp.

21. childhood-onset diabetes.mp.

22. Juvenile onset diabetes.mp.

23. (juvenile adj2 diabet*).mp.

24. Insulin dependent diabet*.mp.

25. juvenile diabetes.mp.

26. IDDM.mp.

27. or/14-26

28. 13 and 27

29. limit 28 to "all child (0 to 18 years)"

30. limit 29 to english language

31. limit 30 to yr="2001 - 2017"

BMJ Open

Primary Outcomes Reporting in Trials of Pediatric Type 1 Diabetes Mellitus: A Systematic Review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014610.R2
Article Type:	Research
Date Submitted by the Author:	30-May-2017
Complete List of Authors:	Khanpour Ardestani, Samaneh; University of Alberta Faculty of Medicine and Dentistry, Pediatrics Karkhaneh, Mohammad; University of Alberta Faculty of Medicine and Dentistry Yu, Hai Chuan; University of Alberta Faculty of Medicine and Dentistry Hydrie, Muhammad Zafar Iqbal; Ministry of health Jeddah region Vohra, Sunita; University of Alberta, CARE Program Dept of Pediatrics
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	systematic review, Pediatrics, diabetes, treatment outcome, Adverse events < THERAPEUTICS

Primary Outcomes Reporting in Trials of Pediatric Type 1 Diabetes Mellitus: A Systematic Review

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Key words: systematic review, pediatrics, diabetes, treatment outcome, adverse events

Word count: 2129

Abstract

Objective: Our objective was to systematically review randomized clinical trials (RCTs) of pediatric type 1 diabetes mellitus (T1 DM) to assess reporting of (i) primary outcome, (ii) outcome measurement properties, and (iii) presence or absence of adverse events.

Methods: Electronic searches in MEDLINE, EMBASE, CINAHL, Cochrane SR, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were undertaken. The search period was between 2001 and 2017. English-language RCTs on children younger than 21 with T1 DM were selected. We excluded studies of diagnostic or screening tools, multiple phase studies, protocols, and follow-up or secondary analysis of data.

Results: Of 11816 unique references, 231 T1 DM RCTs were included. Of total 231 included studies, 117 (50.6%) trials failed to report what their primary outcome was. Of 114 (49.4%) studies that reported primary outcome, 88 (77.2%) reported one and 26 (22.8%) more than one primary outcomes. Of 114 studies that clearly stated their primary outcome, 101 (88.6%) used biological/physiological measurements and 13 (11.4%) used instruments (e.g. questionnaires, scales, etc.) to measure their primary outcome; of these, 12 (92.3%) provided measurement properties or related citation. Of the 231 included studies, 105 (45.5%) reported that adverse events occurred, 39 (16.9%) reported that no adverse events were identified, and 87 (37.7%) did not report on the presence or absence of adverse events.

Conclusion: Despite tremendous efforts to improve reporting of clinical trials, clear reporting of primary outcomes of RCTs for pediatric T1 DM is still lacking. Adverse events due to DM interventions were often not reported in the included trials. Transparent reporting of primary outcome, validity of measurement tools, and adverse events need to be improved in pediatric T1 DM trials.

Strengths and limitations of this study

- This is the first systematic review which evaluates the condition of primary outcome reporting among RCTs of pediatric type 1 diabetes mellitus in an era post CONSORT.
- This study shows reporting of primary outcomes in RCTs conducted on diabetic children is not adequate.
- Reporting of adverse events and measurement properties of outcome measures also need to be improved.
- Knowledge synthesis efforts will be facilitated if heterogeneity in primary outcome selection is reduced.
- This review was restricted to English language, potentially, limiting generalizability of the findings to English literature.

INTRODUCTION

Randomized controlled trials (RCTs) are considered the gold standard to assess efficacy of interventions.(1) To ensure validity of findings in a clinical trial, it is paramount to report a clear set of outcomes, especially the primary outcomes measured, along with measurement tools used, and any assessment of adverse events. Health care professionals, patients, health policy developers and governments expect transparent reporting in trials to make sure the process of decision making is well informed and less biased.(2-4)

The *CONsolidated Standards Of Reporting Trials* (CONSORT) statement, which was initially introduced in 1996 to address the problem of incomplete reporting in the published clinical trials, has been updated twice since, in 2001 and 2010.(5, 6) Clear reporting of a study's primary outcome is essential, as it is used to inform the sample size calculation and is the main driver behind the trial's purpose. If primary outcomes are not reported clearly, the results of the trial may be jeopardized. While 585 journals have endorsed CONSORT since 1996, review studies have shown that primary outcomes were explicitly defined in only 45% and 53% of trial reports that were indexed in PubMed in 2000 and in 2006, respectively.(7, 8) Inadequate primary outcome reporting in pediatric trials has also been reported in some previous studies.(9, 10) To better understand the extent of the problem across fields, we have initiated a series of systematic reviews to assess primary outcomes reporting in trials (PORTal). Our first *PORTal* systematic review highlighted this problem in randomly sampled pediatric RCTs and demonstrated that 27.2% of studies published in high impact journals did not specify their primary outcomes. (11)

Pediatric diabetes mellitus (DM) is an emerging public health concern in the 21st century (12) and appropriate outcome reporting in DM trials is of great importance due to its high prevalence and economic burden worldwide.(13, 14) Reliable assessment of interventions on pediatric DM requires RCTs to be clearly reported.

In addition to clarity in defining primary outcomes, RCTs ought to demonstrate how they measured their primary outcome and whether their measurement tools were valid and reliable.(2, 14)Type and frequency of adverse events occurrence are also important to be studied and reported by RCTs in order to evaluate both the effectiveness of an intervention as well as possible harms associated with it.(5)

Primary objectives of this review were to assess RCTs of pediatric DM, published between 2001 and 2017 to evaluate reporting of (i) primary outcome, (ii) measurement properties of primary outcome measure, and (iii) presence/absence of adverse events.

METHODS

A systematic review protocol has been published at the PROSPERO website (CRD42013005224) (see appendix 1). We followed PRISMA guideline for conducting this systematic review. (15)

Search Strategy

Electronic searches in MEDLINE, EMBASE, CINAHL, Cochrane SR, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were undertaken. Searches were limited to RCT study design, children under 21 years of age, English language, and dated since 2001 (last update Jan 2017). A five-year interval (1996-2001) since the initial publication of CONSORT was applied to our search to allow guideline implementation. The complete search strategy is available upon request to the corresponding author (see appendix 2 for Medline search strategy).

Study Selection

RCTs were selected if they were parallel, cross-over, factorial, and N-of-1 trials studying type 1, and examined any medical and non-medical interventions. Studies were excluded if the population included both children and adults, and if they were diagnostic studies, part of multi-phase trials, protocols, follow-up, and secondary analysis of data. Title and abstracts were screened for relevant entries and then full texts of potential articles were reviewed using pre-specified criteria for inclusion or exclusion. Four independent reviewers (SKA, MK, HCY, MZIH) performed study selection and discrepancies were resolved by consensus; for disagreements, a senior reviewer was sought (SV).

Data Extraction

Using a standardized form, four independent reviewers performed data extraction (SKA, HCY) and verification (MK, MZIH). Collected data included journal name, publication year, design of

the study, age, sex, sample size, disease condition, intervention and comparator(s)of interest, primary outcome(s), outcome measures, measurement tools and their properties, and adverse events. For more investigation, documented journal impact factors (IF) were obtained for the year 2015 (InCites Journal Citation Reports; https://jcr.incites.thomsonreuters.com).

Full text articles were searched for any explicit indication of primary outcome. A variety of terms for the concept of 'outcome' were accepted including 'endpoint', 'variable', 'outcome variable', 'objective', 'pre-specified outcome', 'dependent variable', 'efficacy parameter', or equivalents. If studies clearly stated their primary outcome using the mentioned terminology or described with a synonymous term anywhere in their manuscript, they were considered as "reported primary outcome". We also considered them as "reported", if they explicitly stated the outcome used for the sample size calculation. If studies provided several outcomes without specifying their primary, we considered them as "failed to report primary outcome". After identifying the primary outcome, if it was not a biological/physiological measure (e.g., blood tests), we sought for its measurement tool and reporting of measurement properties (validity and reliability), in addition to any relevant citation(s). Furthermore, any assessment of presence or absence of adverse events (and other relevant terms) was documented. If a study did not report at all on adverse events (its presence or absence), we classified that as "failed to report adverse events of intervention".

Data Analysis

Using descriptive analysis, we presented percentages, mean, median, range, and inter quartile range (IQR) for the primary outcome and adverse events. Since this systematic review focused on reporting status of primary outcome and adverse events in published RCTs and was not intended to evaluate the effectiveness or efficacy of the interventions, the risk of bias and meta-analysis were not part of our study. Considering journals' impact factor (IF) for each published RCT, we grouped them into three batches using first quartile (Q1), interquartile range (Q3-Q1), and last quartile (Q4) of all IFs; journals with no available IF were coded as unknown. Chi-square test was performed for finding the differences between proportions of reporting primary outcome and adverse events among low, medium, and high impact factor journals using Stata statistical software release 14. (16)

Patient involvement

Patients were not involved in the design and conduct of this study as the present study was a systematic review of published RCTs.

RESULTS

Our electronic search yielded 11816 unique references; full texts of 986 potentially relevant studies were retrieved for inclusion/exclusion. Seven hundred and fifty-five out of 986 retrieved articles were excluded; reasons for exclusion are presented in PRISMA flow diagram (Figure 1). Finally, 231 RCTs of pediatric T1 DM were included for this systematic review.

Type 1 Diabetes Mellitus

Of 231 RCTs, 177 (76.6%) had parallel and 54 (23.4%) had crossover groups design. Total population was 21,014 and sample sizes ranged from 7 to 689 participants (Median: 51.5, IQR: 30-110.75). Other general characteristics of the studies are summarized in Table 1. Interventions comprised different forms of insulin therapy, oral medications, dietary, educational, and other medical interventions for glucose monitoring and insulin delivery methods.

Table 1. General characteristics of the included studies

RCTs' Characteristics		Diabetes type 1 RCTs (n=231)
Journals' impact factor	High (≥8.42) Medium (≥2.57 and <8.42) Low (<2.57) Unknown	59 (25.5) 115 (49.8) 42 (18.2) 15 (6.5)
Age range	Range of actual age (years) Range of mean (years)	1-21 2.9-17.7
Type of design	Parallel Crossover	177 (76.6) 54 (23.4)
Sample size	Range Mean (SD) Median (IQR)	7-689 Mean: 91.37 (103.38) Median: 51.5 (30-110.75)

Type of Intervention	Insulin/drug-based Diet-based Education-based Other Medical intervention Others	91 (39.4) 21 (9.1) 41 (17.7) 17 (7.4) 61 (26.4)
Controls	Placebo Usual care/No treatment/Waitlist Other treatment	29 (12.5) 97 (42) 105 (45.5)

* Data are presented as n (%)

Primary Outcomes

Of 231 RCTs, 114 (49.4%) studies explicitly identified their primary outcome while 117 (50.6%) did not. Of the 114 studies that transparently reported a primary outcome, 88 (77.2%) reported one primary outcome, 18 (15.8%) reported two primary outcomes, and 8 (7%) identified between three to seven primary outcomes. Among studies with a single primary outcome (n=88), 83 (94.3%) were biological/physiological measurements, and the rest (n=5, 5.7%) were non-physiological (Table 2). Overall, these trials used 14 uniquely different primary outcomes. Out of 88 studies with single primary outcomes, forty eight (54.5%) measured hemoglobin-A1C and 24 (27.3%) measured blood glucose levels.

Table 2. Frequency & type of primary outcomes in clinical trials of type 1 diabetes mellitus

Outcome categories	**Primary outcomes**	**Frequency* n (%)**
Physiological measures	HbA1C levels	48 (54.5)
	Blood glucose levels	24 (27.3)
	C-peptide levels	4 (4.5)
	Endothelial function	2 (2.3)
	Time to metabolic normalization	1 (1.14)
	Fructosamine levels	1 (1.14)
	Insulin sensitivity	1 (1.14)
	Change in creatinine clearance rate	1 (1.14)
	Epinephrine response to hypoglycemia	1 (1.14)
Non physiological measures	Treatment Fidelity	1 (1.14)
	Perceived diabetes self-efficacy	1 (1.14)
	Preference for NovoTwist versus screw-thread needles in	1 (1.14)

	children and adolescents	
	Health-related quality of life	1 (1.14)
	Macro and micronutrient composition of different diets	1 (1.14)

* Some studies used more than one primary outcome

Outcome Measures

Of 114 studies that clearly defined their primary outcome, 101(88.6%) used biological/physiological measurements including measurements of glycemic control (e.g., hemoglobin-A1c (HbA1c), blood glucose). Thirteen (11.4%) trials used an outcome measurement instrument to measure their primary outcome. Of these 13, five provided both measurement properties and citation for the instruments used; seven provided only the citation and one provided neither.

Adverse Events

Of 231 studies, 105(45.5%) reported adverse event(s) associated with the intervention under study, 39 (16.9%) reported the absence of adverse events, and 87 (37.7%) failed to report on the presence/absence of adverse events.

Journals' impact factor and CONSORT endorsement

Based on quartiles of journals IFs, three levels of low (IF<2.57), medium (2.57≥IF< 8.42), and high (IF≥8.42) were established. There was no statistically significant difference among studies published in low, medium and high IF journals regarding adverse event reporting (P=0.7). However, failing to report primary outcome was associated with publishing in low IF journals (P=0.04) (Table 3).

Considering the date of publication, an upward trend was observed in reporting primary outcome(s) over time (Figure 2). However, endorsing CONSORT guideline did not influence the reporting of primary outcomes. Of 231 included trials, 108 (46.8%) were published in CONSORT-endorsing journals. Among those, 57 (52.8%) reported their primary outcome, while 57 (46.3%) of 123 trials published in non-endorsing CONSORT journals reported a primary outcome (P=0.3). (17)

Table 3. Frequency distribution of primary outcome and adverse event reporting by journals impact factors

Impact factor		Low (n=42)*	Medium (n=115)	High (n=59)	Chi^2 test
Primary outcome	Reported (n=114)	14 (12.3)**	64 (56.1)	31 (27.2)	p-value=0.04
	Failed to report (n=117)	28 (23.9)	51 (43.6)	28 (23.9)	
Adverse events	Reported (n=144)	25 (17.4)	76 (52.8)	39 (27.1)	p-value=0.7
	Failed to report (n=87)	17 (19.5)	39 (44.8)	20 (22.9)	

* Low Impact Factor (<2.57), medium IF (2.57≥IF< 8.42), and high IF (≥8.42); **All data are presented as n (%)

DISCUSSION

This is the first study to present a comprehensive overview of primary outcome and adverse events reporting among published RCTs in pediatric T1 DM.As RCTs are recognized for their importance in medical research, methodological examinations of their reports is crucial for appropriate medical practice.(18)

It has been 20 years since the initial CONSORT statement recommended guidelines for minimal necessary RCT reporting. Since then, reporting of study rationale, objective, recruitment methods, sample size calculation, allocation concealment, and method of sequence generation have been improving among published clinical trials.(19) Nevertheless, we and other groups have shown that reporting of primary outcome, measurement tools and reporting of the validity and reliability of those tools have not been improved alike.(7, 20-22) A systematic review performed on a random sample of pediatric RCTs published in high-impact CONSORT-endorsing journals reported that 27.2% of the trials failed to report any primary outcome.(10)In our analysis, we demonstrated suboptimal reporting of primary outcomes and adverse events of interventions in journals with high and low impact factor, regardless of whether they endorsed the CONSORT guideline or not. We were quite flexible regarding author terminology used to describe primary outcomes in articles. Given that, if authors did not explicitly specify their

primary outcome(s), we considered this issue as a failure in reporting. Failure in reporting primary outcome(s) may lead to selective outcome(s) reporting; (23)CONSORT and its extensions were intended to prevent biased reporting by ensuring primary outcomes are clearly and explicitly stated in all peer-reviewed published RCTs. This also influences the qualitative evaluation of RCTs in systematic reviews and meta-analyses using existing risk of bias tools.(24)Furthermore, heterogeneous outcomes challenge knowledge synthesis efforts to summarize data between trials and maximize its utility in decision-making.

DM lends itself to use of biological/physiological measurements. Accuracy in the measurement of these biological or physiological assessments is outside our scope, but we are reassured that the other instruments used (e.g. surveys) had appropriate citations regarding their measurement properties (reliability, validity). Furthermore, we found heterogeneity in primary outcomes used in our included studies (only half of them used similar primary outcomes). According to the COMET (Core Outcome Measures in Effectiveness Trials) initiative,(25)consistency in primary outcome measurement between trials is necessary to allow for meaningful knowledge synthesis. Most systematic reviews try to assess treatment effectiveness by compiling evidence from multiple RCTs; however, these efforts are hampered by heterogeneity in outcome measurement.

Strengths and limitations:

To our knowledge, this systematic review is unique in that it has evaluated the condition of primary outcome reporting among RCTs of pediatric T1 DM in an era post CONSORT. A robust and systematic methodology was employed including independent and duplicate screening/data extraction using pre-specified criteria and data extraction form. This review was a complement to our previous work that examined a random sample of all pediatric RCTs published in high profile peer-reviewed journals.(11) We further examined primary outcome and adverse event reporting on the basis of high, medium, and low impact factor journals.

As a possible limitation, this review was restricted to English language, potentially, limiting generalizability of the findings to English literature.

Implications:

The results of this systematic review underscore the potential opportunities for improving the quality of reporting in pediatric clinical trials. It is important for journals that endorse

CONSORT to ensure that authors and reviewers use the checklist to confirm reporting of main components of RCTs is complete and transparent. Pediatric DM is an important condition with increasing prevalence and will have global impact on health. To be of most use to clinicians and policy-makers, trials in this field would benefit from improved reporting of primary outcomes and adverse events. In addition, development of a core outcome set (to reduce heterogeneity in primary outcome measurements) and using outcome measurement instruments that are valid and reliable and reported as such are of great importance to support quality meta-analysis leading to more precise and unbiased findings.

Figure 1: Adapted version of PRISMA flow diagram of study selection

Figure 2: Proportion of studies that reported primary outcome(s) by year of publication

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Competing interests

I/We have read and understood the BMJ Group policy on declaration of interests and declare the following interests:

Grant funding for research but no other competing interest

"Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: this study has had financial support from the Canadian Institutes of Health Research (CIHR) for the submitted work; the authors declare they have no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Authors' contribution:

Each of the authors met the criteria for authorship established by the ICMJE. Each author contributed substantial to 1) conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Samaneh Khanpour Ardestani/SKA: Dr. Khanpour Ardestani was substantially involved in design and conduct of the study, screening articles, extracting the data, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Mohammad Karkhaneh/MK: Dr. Karkhaneh was substantially involved in the conduct of the study, screening articles, extracting the data, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Hai Chuan Yu/HCY: Mr. Yu was substantially involved in screening articles, extracting the data, revising the manuscript and final approval of the version to be published.

Muhammad Iqbal Zafar Hydrie/MIZH: Dr. Hydrie was substantially involved in screening the articles, extracting the data, revising the manuscript and final approval of the version to be published.

Sunita Vohra/SV (corresponding author): Dr. Vohra was substantially involved in design and conduct of the study, interpretation of the data, drafting and revising the manuscript and final approval of the version to be published.

Transparency declaration:

"The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

Data sharing statement

The complete search strategy is available upon request to the corresponding author.

Ethical approval:

Ethical approval was not required for this study.

Funding:

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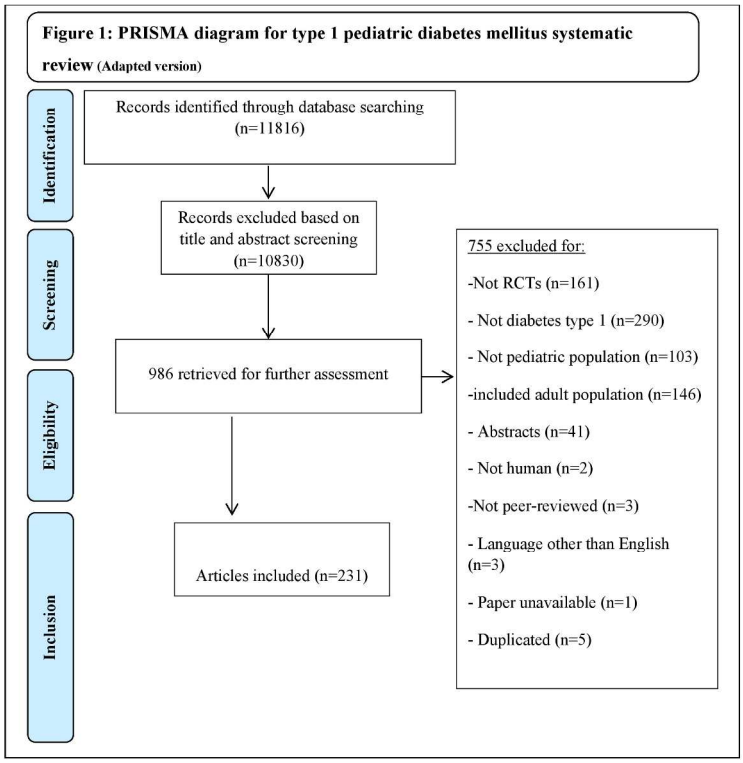

Figure 1: PRISMA diagram for type 1 pediatric diabetes mellitus systematic review (Adapted version)

215x279mm (300 x 300 DPI)

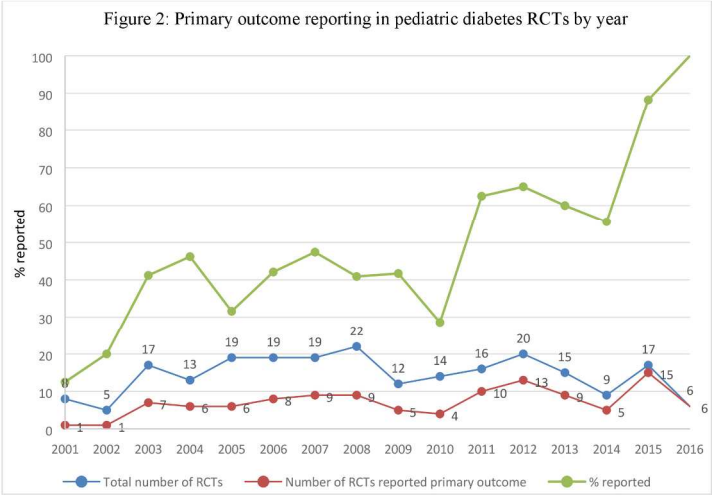

Figure 2: Primary outcome reporting in pediatric diabetes RCTs by year

215x279mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5,6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10,11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11,12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13-15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Systematic review of outcome measures in randomized controlled trails of pediatric diabetes management

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
01/05/2012

4 Anticipated completion date
Give the date by which the review is expected to be completed.
30/06/2016

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	No	Yes
Risk of bias (quality) assessment	No	Yes
Data analysis	No	Yes

Provide any other relevant information about the stage of the review here.

Review team details

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10 Organisational affiliation of the review
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11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

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12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Alberta Innovates Health Solutions; Canadian Institute for Health Research

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
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Dr	Liliane	Zorzela	CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Canada

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

How well were the primary outcomes identified and reported in pediatric diabetes randomized controlled trials?

What were the psychometric properties of the instruments used to measure outcomes in these trials?

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following electronic bibliographic databases are included in the search: MEDLINE, EMBASE, CINAHL, The Cochrane Library, Cochrane SR, and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms were related to diabetes (e.g. diabetes mellitus, juvenile onset). The terms were combined with the MEDLINE filter for randomized controlled clinical trials and pediatrics (under 21 years old). The search terms will be adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where these are

available. The search will be limited to English-language studies. Studies published between January 2001 and May 2012 will be considered.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Diabetes mellitus type 1 results when the pancreas no longer produces significant amounts of the hormone insulin, owing to the destruction of the insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Type 1 diabetes is treated with insulin replacement therapy—either via subcutaneous injection or insulin pump. Treatment of diabetes focuses on lowering blood sugar or glucose (BG) to the near normal range, approximately 80–140 mg/dl (4.4–7.8 mmol/L). Diabetes mellitus type 2 is an intricate metabolic disorder with heterogeneous etiologies and is increasing in prevalence. Social, behavioral and environmental risk factors can trigger the disease in genetically susceptible people. Insulin resistance and insulin secretory failure are the main mechanisms involved in its pathophysiology. Lifestyle modification (nutritional and exercise) beside pharmacological therapy, such as insulin and oral antihyperglycemic medications (e.g metformin) are key management approaches.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Pediatric patients 0-20 years of age.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

We will include any RCTs looking at interventions aimed at managing diabetes (e.g. different insulin regimens, educational therapies, etc). We will exclude diabetes prevention trials as well as trials assessing diabetes diagnostic tools. We will also exclude pilot studies, secondary studies, and studies validating psychometric properties of measurement tools.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Any comparator will be allowed, including placebo and usual care.

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Randomized controlled trials (RCTs) will be included; we will exclude pilot studies, multi-stage trials, trials of diagnostic tools, and secondary reports/follow up studies.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Any setting dealing with pediatric health care will be included.

24 Primary outcome(s)

Give the most important outcomes.

This study aims to assess the quality of reporting, heterogeneity in selecting and validity of outcome measures presented by authors of pediatric diabetes trials. This study will not restrict the outcomes being assessed as the goal is to identify current trends in pediatric diabetes research reporting. Some examples of the outcomes often assessed include glycemic control, as measured by HbA1c levels, as well as insulin doses and hypoglycemic episodes.

Give information on timing and effect measures, as appropriate.

We will not include an assessment of effect or timing.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
None.

Give information on timing and effect measures, as appropriate.
None.

26 Data extraction (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Duplicate articles will be removed prior to review. Two reviewers will then individually screen article titles and abstracts for inclusion. Full text of potentially included articles will be obtained and assessed for inclusion using preset criteria. Data will be extracted by one reviewer and verified by a second reviewer. Where disagreement between reviewers exists, the reviewers will attempt to reach consensus through discussion and a third reviewer will be consulted where necessary. Data to be extracted include: age and gender of participants, study design, condition, interventions and controls under study, details of outcomes and outcome measurement tools, and details of safety/harms assessment.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Because we are focusing on outcome reporting, risk of bias will not be assessed.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
For the purpose of this systematic review data combining may not be feasible. If appropriate, count data will be presented using proportions and will be analyzed using descriptive statistics and Chi-squared tests.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned.

Review general information

30 Type and method of review
Select the type of review and the review method from the drop down list.
Intervention, Systematic review, Other

Methodologic

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Canada

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
We plan to submit a paper to a peer reviewed journal relevant to pediatric diabetic medicine.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
diabetes type 1 or type 2

reporting

outcomes

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Medline search strategy:

1. randomized controlled trial/

2. clinical trial.pt.

3. randomi?ed.ti,ab.

4. placebo.ti,ab.

5. dt.fs.

6. randomly.ti,ab.

7. trial.ti,ab.

8. groups.ti,ab.

9. or/1-8

10. Animals/

11. Humans/

12. 10 not (10 and 11)

13. 9 not 12

14. exp Diabetes Mellitus/

15. exp Diabetes Mellitus, Type 2/

16. exp Diabetes Mellitus, Type 1/

17. type 1 diabetes.mp.

18. type 2 diabetes.mp.

19. diabet*.mp.

20. diabet* syndrome*.mp.

21. childhood-onset diabetes.mp.

22. Juvenile onset diabetes.mp.

23. (juvenile adj2 diabet*).mp.

24. Insulin dependent diabet*.mp.

25. juvenile diabetes.mp.

26. IDDM.mp.

27. or/14-26

28. 13 and 27

29. limit 28 to "all child (0 to 18 years)"

30. limit 29 to english language

31. limit 30 to yr="2001 - 2017"