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COMMENTARY

Randomised Controlled Trials in Diabetes Research: A Pathway to Interpreting Published Results

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Key Summary Points

Randomised controlled trials (RCTs) remain the gold standard for direct treatment comparisons.

However, interpreting the results of RCTs and making judgements about the quality of evidence and how results may be applicable to diabetes management can be difficult for healthcare practitioners (HCPs).

In this article, a checklist of the points that we consider most important when reading and interpreting RCT publications is summarised, and may serve as useful guidance for HCPs.

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INTRODUCTION

Although the importance of real-world evidence should not be underestimated, randomised controlled trials (RCTs) remain the gold standard for direct treatment comparisons. Over the last two decades, numerous publications have presented results of RCTs investigating the safety and efficacy of therapies for the treatment of type 2 diabetes, for example long-acting basal

insulin analogues [1–14]. RCTs such as these use a robust design and methodology that aims to avoid confounders and determine differences between basal insulins. However, interpreting the results of RCTs and making judgements about the quality of evidence and how results may be applicable to diabetes management can be difficult for healthcare practitioners (HCPs) because of differing trial methodologies, analysis plans, and endpoints.

There are guidelines for those developing publications that report the results of RCTs, such as the Consolidated Standards of Reporting Trials (CONSORT) guidelines [15], and readers are advised to familiarise themselves with these if possible. However, we have developed a checklist of points we consider most important when reading and interpreting RCT publications (Fig. 1). This checklist is based on CONSORT, other published literature, and our own experience, and may serve as useful guidance for HCPs. This article will discuss these key points in more detail, progressing through the sections of a typical RCT publication.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CHECKLIST ITEMS

Introduction Section

Does the Publication Provide a Clear Rationale for the Study and Give Specific Objectives or Hypotheses?

When undertaking research involving human subjects, it is essential that there is a clear and justified rationale based on a comprehensive understanding of the scientific literature to avoid unnecessarily exposing people to the risks associated with research [15, 16]. The introduction to an RCT publication should highlight the objectives of the trial, the gaps in the literature that the study would address, its importance to the field, and it should allow the authors to present the hypotheses that are being tested.

The research questions being posed in the introduction of an article are also useful to help clarify whether the RCT has employed the appropriate study design and, if not, the impact this may have on the reliability of the results. A competent RCT research question will encompass the participant population, the therapy/clinical intervention, outcomes, and it typically questions the effectiveness of one therapy versus another (or placebo) [17, 18].

Methods Section

Is the Randomisation Method Reported and Appropriate?

Randomisation in RCTs is critical for ensuring that any known or unknown confounding factors present in the population being investigated are equally distributed, allowing the effects of an outcome to be reliably attributed to the treatment [17]. As such, details of the randomisation procedure should be clearly reported in the methods section of the publication. Most trials will use equal randomisation, in which study groups are randomised in a 1:1 ratio; however, trial participants may be randomised in a 2:1 or 3:1 ratio for reasons including cost, ethics, increased statistical power, and the potential to gain extra information on the treatment [15, 19]. It is therefore good practice to provide the specific randomisation ratio. Additionally, the specific method by which participants are randomised to a given group is important when determining the reliability of the randomisation outcome and the extent to which bias may have been unintentionally incorporated [15]. A technique that provides true randomisation (such as a computerised sequence generator) is recommended, as treatment allocation cannot then be predicted, whereas the use of information such as date of birth to approximate randomisation may lead to selection bias and is therefore not acceptable [15, 17].

Were Participants and Physicians 'Blinded' to the Treatment Being Received/Given?

There are a number of levels in an RCT at which knowledge of the trial and treatments being

INTRODUCTION		
Does the publication provide a clear rationale for the study and give specific objectives or hypotheses? Clinical studies must be justified by a clear rationale, to avoid unnecessarily exposing people to the potential risks of research, and such justification usually involves a summary of the current literature – subsequently, the overall objective of the trial, or even specific hypotheses, should be presented.	**Yes** ☐	**No** ☐
METHODOLOGY		
Is the randomisation method reported and appropriate? The randomisation method should be reported in the methods section of the publication – a technique that provides true randomisation (such as a computerised sequence generator) should be used, whereas use of information such as date of birth to approximate randomisation is not acceptable as it may lead to selection bias.	**Yes** ☐	**No** ☐
Were patients and physicians 'blinded' to the treatment being received/given? Ideally, neither the patient nor the treating physician would know which treatment was being received/given, to avoid bias – this is a 'double-blind' study design.	☐	☐
Was the study conducted in line with the study protocol? Most trials will have a detailed protocol that specified how the trial will be conducted. Deviations from the planned protocol can affect the interpretation or relevance of a study and should be clearly stated in the methods section.	☐	☐
Are all primary and secondary endpoints clearly defined? Primary and secondary endpoints, as well as the statistical methodology used to analyse them, should be pre-defined as per the trial protocol. This information should be clearly presented in the methods, and any analyses that were not pre-defined should be clearly stated as 'exploratory' or 'post-hoc'.	☐	☐
Is the sample size appropriate for the analyses being done? Sample size is usually calculated based on the ability to show a pre-defined and clinically relevant difference for the primary endpoint – the assumptions for the sample size calculation should be provided in the methods.	☐	☐
RESULTS		
Are all patients accounted for in the trial? A trial should clearly show what happened to each participant – for example, who received treatment, who was included in the analyses (participants should be analysed by the groups to which they were randomised, an 'intent-to-treat' analysis), and who discontinued treatment. Ideally, this information should be captured in a flow diagram for clarity, and discontinuations and exclusions should be minimal.	**Yes** ☐	**No** ☐
Were the groups similar at the start of the trial? The more similar the comparator groups at the start of the trial, the better the randomisation process has worked – note that it may not be possible for all aspects to be similar between groups, such as some treatment-specific dosing levels or regimens.	☐	☐
Are the results presented and interpreted in line with the pre-defined statistical plan? Endpoints are often analysed in a hierarchical manner, and the interpretation of results should be consistent with this analysis plan – for example, secondary endpoints can only be statistically analysed or interpreted if the primary endpoint is met.	☐	☐
Are estimates of effect size and precision given? For primary and secondary endpoints, an effect size estimate (such as Relative Risk [RR] or Number Needed to Treat [NNT]) should be given. Estimates of precision (such as confidence intervals [CIs]) should also be provided where appropriate – narrow CIs suggest a high level of confidence that the effect size estimate provided precisely reflects the true population effects size. CIs can also help to interpret statistical significance, as if a CI includes a value corresponding to no effect, then the effect size estimate is not statistically significant at the 0.05 level.	☐	☐
Are adverse events reported? Detailed information about harms or unintended effects should be presented, as this may determine whether an intervention is considered acceptable.	☐	☐
DISCUSSION		
Are the results interpreted and discussed appropriately? The discussion section should provide interpretation that is consistent with the results presented, balancing benefits and harms and clearly addressing trial limitations. Whether the results are generalisable to people outside of the trial should also be discussed.	**Yes** ☐	**No** ☐

Fig. 1 Interpreting publications reporting results from randomised controlled trials (RCTs): a guidance checklist

used can introduce bias, including participants, healthcare providers, data collectors, outcome adjudicators, and data analysts [15]. Unblinded participants may act differently if they are aware of their treatment group, while those involved in trial organisation or data analysis may unconsciously introduce bias through differential outcomes assessments and data analysis strategy choices. Ideally, neither the participant nor the treating physician would know which treatment was being received/given; this is known as a 'double-blind' study design [20]. A process known as allocation concealment should be employed where possible to prevent those managing participant treatment assignment from knowing the allocation in advance, and is an important partner to robust randomisation in preventing unintentional selection bias [15]. Given the importance of being able to evaluate potential biases in an RCT, a clear description of who was blinded and in what manner should be provided. For example, in a study of 40 consecutive RCT publications from five leading journals, eight different blinding combinations were employed in RCTs that reported being double blind [15, 21]. It is important to note that blinding is not always possible in an RCT, and when outcomes are objective (e.g. death), blinding is less important than if outcomes are subjective (e.g. symptoms) [20, 22].

Was the Study Conducted in Line with the Study Protocol?

Most trials will have a detailed protocol that specifies how the trial will be conducted. Deviating from the predefined protocol does not necessarily mean that the study was conducted incorrectly, but such deviations can affect the interpretation or relevance of a study and should be clearly stated in the methods section along with the rationale [15, 17]. Protocol deviations can include failing to obtain the desired number of study participants, changes to the inclusion and exclusion criteria, variations in the provided treatments or interventions, changes to the technologies used, and changes to the duration of the follow-up [17].

Even study endpoints, or the way in which they are assessed, may be changed after the trial has begun [15]. In this instance, it is important that the authors are transparent regarding the changes and that the trial has been properly blinded, because changing endpoints based on unblinded data may introduce bias, compromising the reliability of the results. Such changes may be less of a concern if the trial is an adaptive trial in which accumulating data are used to direct modifications to the endpoints in a manner that conforms to prespecified rules [23].

Are All Primary and Secondary Endpoints Clearly Defined?

Primary and secondary endpoints, as well as the statistical methodology used to analyse them, should be predefined as per the trial protocol [15]. Such definition and robust analysis plans prevent the introduction of multiplicity and subsequent false positives, whereby findings stated as 'significant' occur by chance solely because a large number of tests are performed. For example, if 100 tests are performed, five would be significant at a level of $p < 0.05$ purely by chance. Well-defined endpoints also help to provide a suitable sample size estimation for a sufficiently powered study, which is usually based on the primary endpoint [24]. Relevant information should be clearly presented in the methods, and any analyses that were not predefined should be clearly stated as 'exploratory' or 'post hoc'. While studies can have multiple primary outcomes, this may complicate the interpretation of a study drug's efficacy unless multiplicity is clearly accounted for in the statistical analysis plan [15].

It is also worth noting that a clear description of primary and secondary endpoints, in addition to other methodological details, can help to determine whether results should be compared with those from other RCTs. For example, results from two head-to-head trials investigating the efficacy and safety of insulin glargine 300 U/mL versus insulin degludec 100 U/mL (IDeg) (the BRIGHT trial [10]) and 200 U/mL (the CONCLUDE trial [11]) have recently been published. Comparing the results of these two trials may seem logical, but the primary endpoint of BRIGHT was related to HbA_{1c} reduction whereas the rate of

hypoglycaemia was the primary endpoint in CONCLUDE, so readers should carefully consider this type of information before making direct comparisons.

Is the Sample Size Appropriate for the Analyses Being Done?

Sample size is usually calculated based on the ability to show a pre-defined and clinically relevant between-group difference for the primary endpoint. Typically, the smaller the difference is estimated to be, the larger the required participant population [15]. Statistically underpowered trials may still have some benefit in terms of downstream meta-analyses and if the trial is unbiased, properly reported, and published irrespective of results [25, 26]. However, there is the opposing view that underpowered studies have limited use unless for treatment of rare diseases in which plans for a prospective meta-analysis are predefined or for trials in earlier phases where randomised treatment comparisons is not the only defined goal [27]. As with other study considerations, authors should clearly indicate how sample size was determined in the methods, including the effect size that the study is powered to detect.

Results Section

Are All Participants Accounted For in the Trial?

A trial should clearly show what happened to each participant. This includes who received treatment, who was included in the analyses (participants should ideally be analysed by the groups to which they were randomised, i.e. an 'intent-to-treat' analysis), and who discontinued the treatment [15]. This information should be captured in a flow diagram for clarity, and discontinuations and exclusions should be minimal [20]. It is important that the reason for participant attrition is clearly indicated, as participant loss to follow-up may have a very different impact on trial results to excluding specific participants because of treatment withdrawal or poor adherence, as the latter reasons are more likely to be related to the study treatment [15]. Additionally, the reader should be aware that any losses to follow-up may have a large impact on outcomes analyses in terms of introducing bias, especially if the number of participants with the outcome under investigation is small [20]. It should be noted that if participants are excluded from the trial on the grounds of protocol deviations, this should be communicated in the text with an explanation of the deviation [15].

Were the Groups Similar at the Start of the Trial?

As previously stated, the aim of randomisation is to ensure equal division of any known or unknown confounding factors present in the participant population, meaning that any effects on outcomes can be reliably attributed to the treatment [17]. Generally, the more similar the comparator groups at the start of the trial, the better the randomisation process has worked [20], although it should be noted that it may not be possible for all aspects to be similar between groups, due to factors such as treatment-specific dosing levels or regimens. While effective randomised assignment of participants to treatment groups should theoretically remove any selection bias, it is still possible for some differences between treatment groups to occur by chance, particularly when sample sizes are small [28]. For this reason, it is important to evaluate the baseline characteristics of the comparator groups to determine whether there are any clinically important differences that may need to be considered when evaluating the impact of a treatment on the study group. This information is usually presented in a table where values are supported by ranges or standard deviations of the mean where necessary. Note that significance testing of these baseline characteristics between treatment groups is generally not advised and may be misleading [15, 29]. Statistical testing between groups is a way of assessing whether any differences occur by chance, but if randomisation has been performed correctly then any differences in baseline characteristics between the treatment groups in an RCT are, by definition, due to chance [29]. Instead, the reader of an RCT publication should consider whether any differences observed between groups are

clinically relevant and of a magnitude that may impact the outcomes being assessed in the trial.

Are the Results Presented and Interpreted in Line with the Predefined Statistical Plan?

Statistical testing should be predefined ahead of data analysis in order to eliminate bias caused by choosing tests that may misconstrue the significance of the data, and such tests should be clearly described in the methodology section [17]. An important point for readers to note is that endpoints are often analysed in a hierarchical manner, and the interpretation of results should be consistent with this analysis plan—for example, to avoid problems associated with multiplicity and so-called type 1 error, secondary endpoints can only be statistically analysed or interpreted if the primary endpoint is met [30, 31]. An example of this is demonstrated in the recent SoliMix trial comparing the fixed-ratio combination of iGlarLixi (basal insulin glargine 100 U/mL plus the glucagon-like peptide-1 receptor agonist lixisenatide) with the premix insulin analogue BIAsp 30 (30% insulin aspart and 70% insulin aspart protamine) [32]. A primary endpoint of this study was the noninferiority of iGlarLixi to BIAsp 30 in HbA_{1c} reduction from baseline to week 26. Superiority of iGlarLixi to BIAsp 30 in HbA_{1c} reduction from baseline to week 26 was also an endpoint; however, it was a hierarchical key secondary endpoint that would only be interpreted if the primary endpoint and the key secondary endpoints before it in the hierarchy were successfully met. When a primary endpoint does not achieve statistical significance, secondary endpoints may still be of interest and are useful for generating hypotheses [33], but readers should reflect that results for these secondary endpoints should be considered exploratory and interpreted with some caution.

Are Estimates of Effect Size and Precision Given?

For primary and secondary endpoints, an estimate of the between-group difference (or effect size) such as relative risk (RR) or number needed to treat should be given [20]. These values should be supplemented with estimates of precision (such as confidence intervals [CIs]) where appropriate [15]—narrow CIs suggest a high level of confidence that the effect size estimate provided precisely reflects the true population effect size. CIs can also help to interpret statistical significance, as, in some cases, if a 95% CI includes a value corresponding to no effect, then the effect size estimate is not statistically significant at the 0.05 level [20]. However, CIs are also useful when outcomes do not meet the predefined statistical significance, in which case they may indicate that a clinically important difference cannot be ruled out [15].

The usefulness of effect size estimates and CIs is apparent when individual studies with nominally nonsignificant results are subsequently included in meta-analyses pooling multiple studies. For example, in both the EDITION 3 (insulin glargine 300 U/mL [Gla-300] versus insulin glargine 100 U/mL) and BEGIN Once Long (insulin degludec versus insulin glargine 100 U/mL) RCTs in people with type 2 diabetes, 95% CIs objectively suggested no difference between the treatment arms in confirmed hypoglycaemia occurring at any time of day (based on analyses of incidence in EDITION 3 and rates in BEGIN Once Long) [1, 9]. However, in both cases, the upper CI only crossed 1 (which indicated no effect) by a small margin, as the RR was 0.88 (95% CI 0.77–1.01) in EDITION 3 and the rate ratio was 0.82 (0.64–1.04) in BEGIN Once Long [1, 9]. Later, meta-analyses including these studies would show that both Gla-300 and IDeg provided a benefit over insulin glargine 100 U/mL in terms of hypoglycaemia, with similar effect sizes to the individual studies but narrower CIs: 0.91 (0.87–0.96) and 0.83 (0.74–0.94), respectively [34, 35].

Are Adverse Events Reported?

Understanding the potentially harmful effects of a treatment is as important to a reader as understanding the positive benefits the treatment may offer [15]. The analysis of certain events, such as hypoglycaemia in RCTs of diabetes therapies, will be captured within the primary and secondary endpoints and should be reported as described above. However, all adverse events should be closely monitored and clearly reported in the results section of the RCT

publication, typically using a detailed table to break down the adverse events experienced and the proportion of the participants who experienced them in each treatment group [36]. The number needed to harm may also be reported [37]. The data recorded during an RCT concerning harms or unintended side effects is key to determining whether an intervention is deemed acceptable for use [15]. The publication should report the criteria for event confirmation, method of data collection, number of participants withdrawn due to adverse events (whether treatment-related or otherwise), and the absolute risk of each event, where possible [36].

Discussion Section

Are the Results Interpreted and Discussed Appropriately?

The discussion section of an RCT publication should provide interpretation that is consistent with the results presented, balancing benefits and harms and considering the importance of the findings in view of the current published evidence (some of which will have been presented in the introduction) [15]. The main focus should be on the primary endpoint, as this is the outcome considered to be the most important in the context of the study [24]. Secondary endpoints are discussed also, albeit with less importance, and exploratory endpoints, while not typically a focus, can be included for introducing new hypotheses [30]. Whether the results are generalisable to people outside of the trial should also be discussed, as RCT inclusion criteria are often restrictive [15]. Finally, while often excluded, it is important for RCTs to clearly address any trial limitations that may affect the results [15]. These include, but are not limited to, the available participant population, the type of study being performed, and whether there were any study design considerations.

Other Information Provided

While the sections above comprise what we believe to be the key aspects to consider when interpreting the content of an RCT publication, other information should be provided that may reassure the reader that the authors (and, if applicable, the sponsor) are committed to high-quality, transparent scientific communication.

Clinical trial registration is important to ensure that there is sufficient transparency around how a clinical trial is conducted and that data reporting is not biased or selective [15, 38, 39]. Moreover, the International Committee of Medical Journal Editors (ICMJE) recommends that journals require clinical trials to be registered in a public trials registry at or before the time of first patient enrolment in order to be considered for publication [39]. Registration in these databases requires the provision of key information prescribed by a 24-point checklist, including but not limited to primary and secondary outcomes, completion dates, ethics, sponsor information, interventions, study type, and sample size [39]. As such, clinical trial registry pages can be a valuable source of key information that may not all be available within associated publications. Publications reporting results from a clinical trial without a registration number in a reputable registry system should be considered carefully.

Publications will typically include a list of potential conflicts of interest (COIs) for the authors of the article. This is essential for complete transparency regarding any potential biases or influences (e.g. financial gain) that may influence the work [40]. It is important to note that the presence of a potential COI does not necessarily indicate that the results being presented are compromised, and it is up to the reader to evaluate these conflicts and determine whether they believe there to be a COI that impacts the credibility of the results.

CONCLUSION

RCTs are extremely robust when conducted and reported appropriately, but determining whether this has been done and assessing the validity of RCT results can be confusing for individuals who may be unfamiliar with their interpretation. Guidelines regarding RCTs are specific in their intended use. For example,

CONSORT is a guide to reporting the results of RCTs, while developing the trial protocol itself is covered by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [41]. These two guidelines may have some overlapping content but they are designed with different target audiences in mind. Similarly, the checklist presented in this commentary has been developed primarily for clinicians who will be reading RCT publications. It distills the extensive information provided by CONSORT, in addition to other published literature and our own experience, into a refined checklist of key points specifically focusing on the interpretation of results from RCTs (Fig. 1). This checklist can be used alone or in conjunction with other aids such as CONSORT to help HCPs evaluate the quality of evidence provided by RCT publications.

In summary, with the checklist provided, and the explanation of why we consider the points discussed above to be worthy of attention, we hope that this article will provide a useful guide for HCPs when reading and interpreting publications that report results of RCTs.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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