Writing the Discussion Section of a Clinical Paper: A Case Study of Cardiovascular Hypercholesterolemia Research

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ABSTRACT
Situating findings within the subfield is considered an influential part of clinical research studies, yet there are limited resources that demonstrate how it can be effectively achieved. This study extracts recommendations from three writing guides and compares them to samples of discussion sections within successful clinical research studies. On a case-by-case basis, this paper reflects how writers incorporate contextual information within discussion sections and how they may deviate from conventional guidance to situate their findings effectively.

Keywords: contextualization, situating findings, clinical research, discussion, writing

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INTRODUCTION

Prospective clinical trial researchers often struggle with situating findings in their subfield field in clinical research write up. In a matter of a few paragraphs of the discussion section, the reader should be able to draw an understanding of how the research stands in relation to previous clinical trials and nationally-issued guidelines. While many writing guides provide a checklist of information and briefly elaborate on the meaning of each item, few draw attention to the deeper challenges encountered by practitioners: questions about what types of information to develop, discount, or spotlight and when deviations are acceptable or preferred. These considerations are further complicated by constricted space in the discussion section (see Appendix A). In this paper, I aim to understand how researchers use contextual information to situate their findings in their subfield in the discussion section of prospective clinical research papers.

METHODOLOGY

In this paper, I extracted guidelines and recommendations specific to writing the discussion section of prospective clinical trials from three main sources:

I. “Writing Manuscripts Describing Clinical Trials: A Guide for Pharmacotherapeutics Researchers'' by Gary E Pakes
II. “Writing up your clinical trial report for a scientific journal: the REPORT trial guide for effective and transparent research reporting without spin” by Bandolm et al
III. “CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials” by the CONSORT group (Consolidated Standards of Reporting Trials); Moher et al

This paper will focus on how researchers use contextual information, which I will analyze across two categories: (a) research by other practitioners in the subfield and (b) guidelines issued by nationally-accredited agencies. Within each category, I will correspond recommendations from the 3 writing resources. I will then corroborate these patterns by iteratively weaving examples of discussion sections from successful clinical researcher reports.

With regards to how I chose examples to include, I started by eliminating confounding variables: (1) trial phase, (2) trial purpose, (3) drug evaluation, and (4) condition of interest. The data set includes 5 examples of phase III clinical trials that evaluate the safety and efficacy of evolucomab as treatment for hypercholesterolemia. The subfield relevant to the examples in this paper is prospective dyslipidemia cardiovascular research. Appendix B lists the papers considered in this paper.

RESULTS

I. Contextual Research - Validating or contradicting inferences from field findings

Investigator and clinician reader seek to understand how the results of the present trial relate to the field. Two writing guides iterate the importance of providing this information. Pakes claims that the writer needs to show how the researcher's interpretation of the results of the study "agree or contrast with previously published work" [5]. The CONSORT guide asserts how to refine the delivery of this information to be objective. It argues that the presentation of the results in relation to other trials "can best be achieved by including a formal systematic review in the results or discussion section of the report." [7].

When a researcher conducts such a pre-study 'systematic' review, they are able to develop an inference for what their results could demonstrate. Then in the discussion section, they would explicitly suggest whether their findings reprise or contradict the inferences. We will entertain two of the possible scenarios outlined by Pakes: the results of the study "agree or contrast with previously published work" [5].

Not every researcher in the sample set drew inferences from contextualizing information. The summarized list, separated by scenario, is in Appendix C.

IA. Scenario A: The contextual research validates the present study's findings

If the contextual information validates the study's result, then it suggests that it was not due to chance or a singular, isolated instance. Rather the investigators are able to argue that their hypothesized effect of the primary endpoints (the main clinically-relevant statistic of interest) have been clinically observed by other practitioners. Thus, their conclusions are introduced as another revelation of a meaningful trend.

Every researcher in the sample set that drew inferences from contextual information observed at least one inference validated their trial's primary endpoint (see Appendix C). For instance, Blom D.J. et al 2014 first summarizes the results of the primary endpoint - that evolocumab treatment "resulted in a relative reduction in LDL cholesterol levels." Immediately following a few lines of analysis, Blom cites the previously published 2014 OSLER trial (Open-Lab Study of Long-Term Evaluation against LDL-C) to support that primary endpoint, stating the results were "similar" to his own. Similarly, after reporting an increased rate of PCSK9 levels after evolocumab administration, Blom states that his "findings are also in keeping with a number of other trials."

Comparably, Raal F.J. et al 2015 cites published clinical studies to support relevant observations. Raal's familial hypercholesterolaemia study found some patients with "mutations in both LDL receptor alleles" even though those subjects were "thought to have heterozygous familial hypercholesterolaemia." However, he did not present this observation as an isolated case, immediately following that the "result is consistent with recent findings by Sjouke and colleagues in a Dutch Study." Later, Raal even compares his work with other studies that explore the link between the primary endpoint of his study (LDL level) and another condition - coronary artery disease, explicitly stating that his findings were "notably (...) in agreement with previous studies" [6].

Blom and Raal candidly spotlight how sections of their clinical results reproduce previous peer-reviewed observations. The reader learns that the investigators' findings are not anomalies but rather evidenced by other credible sources, drawing credibility to the presented arguments. The writer then builds a credible foundation for subsequent analysis and situates themselves among practitioners in their discipline.

While Pakes' recommendation of using "previously published clinical studies" [5] worked for Blom and Raal, the same type of contextual information is not necessarily used by all writers. We observe differentiation in the types of outside information the researchers cite to achieve the common objective of bolstering the credibility of their observation.

For instance, Robinson et al 2014 deviates from Pakes' recommendation. After identifying that "neurocognitive events were uncommon" in his trials, he directly cites "data from an ongoing, longer term" study that was not published at the time. Despite deviating from the specific requirements of Pakes' writing guide, Robinson's work still demonstrates that citing any evidence to suggest reproducibility of findings is helpful. The approach is riskier since the released data did not yet pass through the peer review process and the argument surfaces as his interpretation of another researcher's data. However, the inclusion of such evidence nonetheless elevates the credibility of his argument as opposed to an analysis section void of any supporting evidence.

Kiyosue et al 2016 also deviates from the other studies. He cites molecular evidence that "suggests that plasma Lp(a) and LDL particles compete for uptake by the LDL receptor." The contextual

article Kiyosue utilized contains no traces of clinical methods and relies purely on biochemical observations. Notably, at the time Kiyosue published his clinical research paper, the mechanism of his primary endpoint (PCSK9 inhibition reduced Lp(a)) "remain[ed] to be fully elucidated." He was thus able to draw upon "recent" molecular evidence to "explain the greater Lp(a) reduction in YUKAWA-2", directly drawing upon the resource to infer the behavior of the "fewer LDL particles to compete with Lp(a)" [3].

The strategies used by Robinson and Kiyosue demonstrate that there is a gradient scale for the types of contextual evidence used to advance a finding - they need not be published or clinical data. A molecular mechanism still reveals that findings are scientifically-founded despite lacking the certainty that it applies to humans. Unpublished data from ongoing trials suggest that a similar phenomenon has been observed before even though claims lack the validity enforced by the peer review process.

IB. Scenario B: The contextual research differ from the present study's findings

The researcher develops an inference after a formal systematic review of contextual information. The CONSORT guide suggests that these inferences should be based on a review that is "as comprehensive as possible, rather than being limited to studies that support the results of the current trial" [7]. Indeed, the researcher may determine that the developed inferences are different from the clinical trial's outcomes. In this scenario, they may employ contextualization to clarify the discrepancy. This approach is useful since the writer preemptively and directly addresses any inconsistencies a reader may otherwise uncover on their own.

In Raal F.J. et al 2015, we find two examples of trial results that deviate from the researcher's expectations developed by reviewing field-findings. The first instance we observe is when Raal concluded that their trial reflected evolocumab response in their tested population to "a greater degree" than previously reported in other studies. This observation of difference allowed him to introduce the conclusion that linked his primary endpoint (LDL cholesterol response) with an ulterior trend in his paper (response was negatively "related" to the "number of alleles associated with receptor negative activity") [6].

In this manner, authors placed in the same scenario as Raal may utilize external evidence to strengthen the uniqueness of their claim. They may specify that their work demonstrates a stronger observed relationship. Notably, Raal clarifies that his results don't entirely conflict with previous work, stating that "this idea is supported by previous studies." Instead he interprets his results as illustrating an earlier trend to a "greater degree," phrasing the results as a clear example of a previously captured trend [6].

The second example of a discrepancy between trial results and contextual inference in Raal F.J. et al 2015 follows directly after the first instance. Raal claims he found an "unexpected(...)" observation ("patients with receptor-negative mutations respond[ed] equally well to treatment as those with

defective mutations"). He interprets this observation as 'unexpected' because the inference for one group (genetic homozygous familial hypercholesterolemic) contradicts the expectation he developed by examining previous results for another group (genetic heterozygous familial). He instrumentalizes the unforeseen nature of the discrepancy to argue that the "trial has clinical implications" in that it qualifies when genetic analyses may be "helpful" for predicting response to evolucomab [6].

Even if they don't perfectly match, writers have the leeway to draw meaningful connections between contextual information and their trial results. The observation of an exaggerated trend may be interpreted by the writer as a 'clear' example, like in the first example from Raal. Similarly, a contradiction may be explored further in research and writing until the previous precedent is qualified, like in the second example from Raal. However, Bandholms notes that throughout the report, the investigator must actively "avoid unintentional reporting or spin biases" [1].

II. Contextual Guidelines - Situating findings using subfield-specific metrics and procedures

The contextual information a researcher incorporates may include clinical guidelines published and regularly reviewed by established institutions. Bandholm's writing guide stipulates the importance of adhering to national guidelines for clinical trials and data [1].[1] And the CONSORT guide maintains that the "[a]ssessment of healthcare interventions can be misleading unless investigators ensure unbiased comparisons'' [7]. By analyzing the discussion sections in the sample set, we see how clinical protocols may be utilized since their objective metrics situate results within the specialized sub-field (see Appendix D).

For example, Robinson et al 2014 specified that he administered statin doses "consistent with the moderate and high intensity statin therapy recommended in the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines." The researchers used this statement as a foundation before they elaborated on the comparative implications of using placebo versus evolocumab [8]. This strategy enables readers (which includes other clinical investigators) to cross-compare results between studies within the subfield because the discussion utilizes a nationally-followed metric for efficacy evaluation. And given that the 2014 study used the most recent protocol (from 2013), the readers learn that the methods were up-to-date and compliant with the updated standards of the subfield.

We observe different types of deviations in how researchers handle using these national guidelines. In this study's data set, Blom D.J. et al 2014 contextualizes the "target" metric (LDL cholesterol level of less than 70 mg per deciliter) was used to measure a favorable result in over "80% of patients." Blom starts by acknowledging that the ACC/AHA "change[d]" the cholesterol guideline to "recommend[ing] that the intensity of therapy be guided by cardiovascular risk rather than by LDL cholesterol goals." He effectively conceded that the metric used to measure the favorable

[1] National guidelines are not past clinical research trials that researchers can use to draw inferences. Thus, they do not qualify as the type of contextual resource that falls under the first subpoint of the results section in this paper.

results was outdated even at the time of writing the paper. He then contends that "despite this recommendation" the metric used in his study "remains a treatment target for patients at very high risk for cardiovascular disease in many countries" [2].

Writers may incorporate analysis similar to Blom D.J. if they are using a metric that deviates from the standard guidelines issued by an established organization. By acknowledging that these guidelines exist, the investigator shows that they are informed about standard practice and situate themselves in their field. If they choose to deviate from the predefined metric, then they may explain why their choice is reasonable, citing relevant clinical use.

Alternatively, an investigator's research may reveal that the guidelines themselves require re-evaluation. In this scenario, the contextual guidelines are modified by the researcher's interpretation of the trial results. Koren M.J. et al 2014 argues that the ACC/AHA initially "tried to simplify" lipid management by "emphasizing statin use" even though the guidelines "acknowledge[d] the limits of statin therapy." Subsequently Kore states that in Section 6.3.2 they "recommended nonstatin therapies (...) when patients remain at high risk despite statin therapy." Interestingly, he then claims that the ACC/AHA "guidance will likely require reevaluation" given the "large LDL-C reductions produced by evolocumab" and investigational medicines [4].

Koren's paper provides an example of trial results being used to recommend modifications to the national clinical guidelines. The discussion section may be utilized for such arguments. Not only will the writer demonstrate a grasp of the current protocol, but they also acknowledge whether their observations suggest revisions. In turn, they situate themselves among other practitioners in the subfield by engaging with the work of an accredited, nationally-followed authority.

DISCUSSION

Critically, when a clinical investigator begins writing their research paper, they must consider that they are not contributing to a vacuum. Readers will probe their adherence to accredited guidelines, dissect their results with regard to previous studies, and scrutinize the accuracy and novelty of their analysis. Researchers who demonstrate that their study impartially and holistically interprets findings in relation to others will be better equipped to situate their work within the subfield of interest. They should therefore review studies that accentuate and differ from their results, utilizing the discussion section to contribute objective and transparent conclusions. Ultimately, these findings will build the groundwork for future investigation, making it all-the-more paramount to incorporate effective contextualization within the discussion.

There are several limitations in this study. The sample size used is quite small ($n=5 < 30$), making the conclusions in this study statistically unreliable. However, the intention of this paper was not to validate claims against the entire field but rather draw meaningful patterns and lessons from sample studies that meet two reliable criteria: (a) representative of work in the broader field and (2) generally successful reports. Also, the data in this study was constrained to a specialized subset

along the parameters of a particular drug, condition, purpose, and phase of clinical trial. Even though the internal validity may be reliable, the external validity of the findings has been compromised. At face value, the findings are not generalizable. However, this report was not developed with the intention of being a statistical meta-analysis but rather a meaningful guide for writing in clinical research.

Future work could use larger sample sizes to draw similar comparisons across phase I and II trials and furthermore compare the types and concentration of information that composes each discussion section. Additionally, many journals have unique requirements regarding the length, level of detail, and layers of analysis to include. Extracting *intra* and *inter*-journal comparisons would also further develop a practitioner's understanding of how to develop the discussion section based on the context. This analysis, however, was beyond the scope of the research question in this paper.

CONCLUSION

By analyzing a sample of Phase III clinical research trials that evaluate the safety and efficacy of evolucomab for the treatment of hypercholesterolemia, we see examples of how researchers use contextualization to demonstrate clinical relevance. We observe that the types of information included to achieve this goal varies on a case-by-case basis and practitioners may find modifying rather than formulaically adhering to these strategies enhances their report. We conclude that incorporating these elements refines the discussion section of prospective clinical research papers by situating the study's findings among the latest research. Ultimately, the contextualization is effectively used when it advances, revises, corrects, or situates arguments introduced by other practitioners and guidelines established by accredited agencies.

Appendix A

Length

The CONSORT guide and Bandholm do not quantify the ideal length of a discussion section. Rather, they chose to describe the phenomenon using general language. The CONSORT guide recommends that authors use "brief" synopses, summaries, and implication sections [7]. Similarly, Bandholm asserts that it is "essential" to make the discussion "concise" and "valuable" to provide brief summaries of statistical results in the written discussion section [1]. Pakes, on the other hand, specifies that "[i]n the discussion section, the writer should try to present in five or six paragraphs"[5].

The samples do not stringently reflect Pakes' statement as a fixed rule but rather ball-park their lengths to the specified range and perhaps deviate based on journal-constraints as opposed to an abstractly-defined "ideal" range. We notice that in general, the studies have studies that tend to go over and not under this requirement. Although the sample size considered in this study is quite small ($n=5 < 30$) and solely limited to phase III studies, if this trend were validated in a larger randomly-chosen sample, the findings would echo a commonly encountered trend; clinical researchers are tasked with including extensive amounts of information in the discussion section and thus resort to longer write-ups. This analysis further develops why many guidelines emphasize and later re-emphasize the importance of brevity and concision amid a string of items that must be included in the discussion section.

Chronology

CONSORT, Pakes, and Bandholm make no reference to how information should be ordered. Note that it is perfectly reasonable to alter the chronology of information in the intermediary paragraphs. Practitioners writing a discussion section may find that certain elements require explanation before others or may be of greater importance than another.

This analysis may influence evaluations of the extent to which authors must delineate descriptions or strip analysis.

Appendix B

#	Author/ Year	Phase 3 Trial Report Title	Paper Length (# Pages)	~ # Pages for Discussion	Discussion Length (# Paras)
1.	Blom, D. J. et. al 2006	A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia	11	1	7
2.	Kiyosue et al 2016	A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk	8	1	6
3.	Koren, M. J. et al 2014	Anti-PCSK9 Monotherapy for Hypercholesterolemia: The MENDEL-2 Randomized, Controlled Phase III Clinical Trial of Evolocumab	10	1	7
4.	Raal, F. J. et al 2015	PCSK9 Inhibition with Evolocumab (AMG 145) in Heterozygous Familial Hypercholesterolaemia (RUTHERFORD-2): A Randomised, Double-blind, Placebo-controlled Trial	10	1	6
5.	Robinson, J. G. et al 2014	Effect of Evolocumab or Ezetimibe Added to Moderateor High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia: The LAPLACE-2 Randomized Clinical Trial	13	1	8

Appendix C

Description	Blom D.J. et al 2014	Kiyosue A. et al 2016	Koren, M.J. et al 2014	Raal, F. J. et al 2015	Robinson, J.G. et al 2014
Contains contextualized inference	Yes	Yes	No	Yes	Yes
Scenario A: Some contextualized inference validates results	Yes	Yes	-	Yes	Yes
Scenario Ai: Uses previously published literature to validate results	Yes	Yes	-	Yes	No
Scenario Aii: Uses ongoing clinical study to validate results	No	No	-	No	Yes
Scenario Aiii: Uses non-clinical evidence to validate results	No	Yes	-	No	No
Scenario B: Some contextualized inference contradicts results	Yes	No	-	Yes	No

Appendix D

Description	Blom D.J. et al 2014	Kiyosue A. et al 2016	Koren, M. J. et al 2014	Raal, F. J. et al 2015	Robinson, J. G. et al 2014
Cites national guidelines	Yes	No	Yes	No	Yes
Guidelines are stated to influence protocol	Yes	-	No	-	Yes
Guidelines are stated to contradict protocol	Yes	-	No	-	No
Guidelines are re-evaluated by authors using trial results	No	-	Yes	-	No

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