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Bias was reduced in an open-label trial through the removal of subjective elements from the outcome definition

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Abstract

Objective: To determine whether modifying an outcome definition to remove subjective elements reduced bias in a trial that could not use blinded outcome assessment.

Study Design and Setting: Reanalysis of an open-label trial comparing a restrictive vs. liberal transfusion strategy for gastrointestinal bleeding. The usual definition of the primary outcome, further bleeding, allows subjective clinical symptoms to be used alone for diagnosis, whereas the definition used in the trial required more objective confirmation by endoscopy. We compared treatment effect estimates for these two definitions.

Results: Fewer subjective symptom-identified events were confirmed using more objective methods in the restrictive arm (18%) than in the liberal arm (56%), indicating differential assessment between arms. An analysis using all events (both subjective and more objective) led to an odds ratio of 0.83 (95% confidence interval [CI]: 0.50−1.37). When only events confirmed using more objective methods were included, the odds ratio was 0.50 (95% CI: 0.32−0.78). The ratio of the odds ratios was 1.66, indicating that including unconfirmed events in the definition biased the treatment effect upward by 66%.

Conclusion: Modifying the outcome definition to exclude subjective elements substantially reduced bias. This may be a useful strategy for reducing bias in trials that cannot blind outcome assessment.

Keywords: Bias; Open-label trial; Blinding; Outcome assessment; Randomized controlled trial; Cluster-randomized

1. Background

Blinded outcome assessment is a key component of randomized controlled trials, as unblinded assessment can result in substantial bias in the estimated treatment effects [1−7]. However, blinded assessment can be difficult to achieve under some circumstances. For example, TRIGGER (Transfusion in Gastrointestinal Bleeding) was an open-label cluster-randomized trial that assessed the feasibility of implementing two red blood cell transfusion strategies (restrictive vs. liberal) in patients admitted to UK hospitals with acute upper gastrointestinal bleeding (AUGIB) [8−10]. The primary clinical outcome was an episode of further bleeding arising from the patient's upper gastrointestinal tract. In open-label trials, blinded outcome assessment can often be achieved by having a third party (e.g., another clinician at the hospital) who is unaware of treatment allocation assess the patient, or by sending the relevant information to a central (blinded) adjudication committee for assessment. However, neither of these options was feasible in TRIGGER [11]. Because cluster randomization was used, every clinician within each trial site was aware of the treatment allocation in that hospital, and therefore, having a third party assesses the patient directly was impossible. Equally, it was not possible to compile relevant information in a blinded manner for review by an independent adjudication committee [11]. Therefore, assessment of further bleeding could not be done in a blinded manner in TRIGGER.

There is little guidance on methods to reduce the risk of bias when blinded outcome assessment is infeasible. One

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What is new?

Key findings

- Blinded outcome assessment in clinical trials is not always feasible, but including subjective elements can produce bias in estimated treatment effects.
- We modified the outcome definition of further bleeding in an open-label, cluster-randomized trial of gastrointestinal bleeding to omit subjective elements, resulting in a definition using more objective measures.
- Reanalysis of the trial data set found that the modified definition which excluded subjective elements reduced bias by up to 66%.

What this adds to what was known?

- Modifying the outcome definition to exclude subjective elements can reduce bias when unblinded assessment is unavoidable.

What is the implication and what should change now?

- Modifying trial end points to exclude subjective elements can be a useful strategy when designing open-label trials where blinded outcome assessment is not possible.

approach would be to modify the outcome to make it easier to implement blinded assessment. However, in some circumstances, the only modification that is possible is to use a surrogate measure in place of a clinically important outcome. Surrogate measures are not always useful indicators of clinical benefits or harms and may not be directly relevant to patients or clinicians [12,13]. For example, the occurrence of a further bleeding episode in TRIGGER could have been based on biomarkers, such as a drop in a patient's hemoglobin count, which could easily have been adjudicated by a blinded committee. However, this may be a misleading surrogate for further bleeding because the count may not change during the acute phase of hemorrhage and therefore would have been of limited clinical relevance.

An alternative approach is to modify the outcome definition to make it less subjective, which can reduce bias while retaining the clinical value of the outcome measure [11]. This second approach was used in TRIGGER. The definition of further bleeding was modified from that used in routine clinical practice to exclude subjective elements. The resulting definition only included more objective measures of further bleeding [11].

We assessed whether modifying an outcome definition can reduce bias using TRIGGER as a case study. We reanalyzed the TRIGGER trial to compare two outcome definitions, the usual definition, which included subjective elements, and the modified definition used in TRIGGER, which excluded subjective elements.

2. Methods

2.1. Choice of outcome measure in TRIGGER

TRIGGER (ISRCTN 85757829) was a cluster-randomized trial that compared the feasibility of implementing two red blood cell transfusion strategies for patients admitted to UK hospitals with AUGIB. In both strategies, patients received a transfusion when their hemoglobin dropped below a certain level, which was 8 g/dL under the restrictive transfusion policy and 10 g/dL under the liberal transfusion policy. It was impossible to blind the trial personnel as the intervention involved blood transfusion in an emergency setting. Our previous publication explains why a blinded outcome assessment was not feasible [11]. The standard of care for managing a patient with AUGIB is resuscitation and stabilization, followed by direct visual inspection of the upper gastrointestinal tract with a fiber optic telescope, called an endoscopy, to identify and treat the source of bleeding.

The primary clinical outcome was further bleeding up to day 28. It was defined as either ongoing bleeding at the end of the initial endoscopy or a bleed that restarted after stopping, as per standard international consensus criteria [14]. Further bleeding can be assessed either using a patient's physical signs and symptoms, or by a visual inspection of the upper gastrointestinal tract using endoscopy. Assessment based on patient symptoms considers hemodynamic instability (e.g., low blood pressure and an increased heart rate), a drop in the hemoglobin concentration, whether the patient has vomited blood, and the passage of altered blood per rectum. In visual inspection, the patient's upper gastrointestinal tract is examined during an endoscopy to determine whether there is ongoing bleeding in the stomach.

We consider an outcome to be subjective if (1) its assessment depends on the judgment of the assessor; and (2) this judgment may be influenced by knowledge of the patient's treatment assignment [15]. Assessment of further bleeding based on patient symptoms inherently involves a degree of subjectivity. For example, signs of hemodynamic instability can be mimicked by other conditions such as sepsis, dehydration, or intercurrent illness. The clinician must judge whether the hemodynamic instability is caused by further bleeding or something else. The hemoglobin concentration may drop because of a delayed response following the initial bleed, hemodilution after fluid infusion, another factor, or a combination. Again, the clinician must judge the cause of the concentration drop. If a patient vomits altered blood (''coffee grounds'' rather than fresh red blood) or passes dark altered blood per rectum (which can often persist for up to 5 days after the initial bleed),