CLINICAL INVESTIGATION

EDITORIAL

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"Using transfusions as a sole means of meeting clinical trial eligibility criteria poses serious risk to both the current and future patients for which the therapy is being tested."

'Tweaking' potential research participants to meet clinical trial eligibility criteria: ethical concerns and scientific implications

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In October 2010, we reported on an interesting clinical practice phenomenon in a Letter to the Editors of the *New England Journal of Medicine* [1]. In three separate clinical oncology studies, during the past year, it was discovered that select patients were being transfused blood products for the sole purpose of meeting inclusion criteria for enrolment in a clinical trial. These cases were detected after the recent introduction of prospective screening of all blood product requests by blood bank technologists at our institution, in attempts to promote the appropriate use of blood transfusion. Of note, in each case, the patients were young and dealing with advanced malignant disease that had failed all available therapies. The purposes of the letter were: to report on this practice and to determine if these were anomalous events or perhaps indicative of more frequent but unreported phenomena; and to outline what we felt were the ethical concerns raised by this practice. Unsurprisingly, we received a wide range of responses to our original letter. Many supported our concerns about the increased risk to patients and the potential adverse impact of the scientific findings when such a practice is tolerated; however, there were also responses that were critical of our recommendations. This article contribution provides us with an opportunity to further explore the implications of the practice we observed and hopefully continue this important ethical conversation.

The ethical dilemma: how common could 'tweaking' with transfusion for clinical trial enrolment be?

In follow-up to our original article, we were interested in determining the frequency in which laboratory values that were modifiable by transfusion were included as part of eligibility criteria for clinical trials, specifically for oncology trials, given that this was the context of our original three cases. Our review focused on trials that used eligibility criteria with targeted values for hemoglobin, platelet and/or albumin levels. Concerns by our institutional research ethics board over contract privacy issues prevented us from reviewing the detailed study protocols for clinical trials currently recruiting at our hospital. Instead, we used the Ontario provincial oncology trial registry as a representative data source [101]. On the date of data abstraction (2 December 2010) a total of 479 clinical trials were listed in the registry under 45 different cancer types. We analyzed treatment trials currently recruiting subjects for three cancer types (n = 296): breast (n = 113), prostate (n = 94) and lung (n = 89). A summary of analysis is presented in Table 1.

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Table 1. Ontario Cancer Trial Registry: transfusion modifiable levels stipulated for eligibility in a clinical trial.

Disease site (number of trials)	Total number of treatment trials	Number of treatment trials with a specified requirement for hemoglobin, platelet or albumin (%)	Number of treatment trials specifying hemoglobin levels by range (g/l)		Number of treatment trials specifying platelet levels by range ($\times 10^9$)		Trials explicitly stating whether blood transfusion was permitted to meet eligibility
			Range	n	Range	n	
Breast (n = 113)	88	36 (41%)	80–89	2	25–49	0	2 (one study stipulated 'No transfusions within 7 days prior to screening')
			90–99	17	50–99	2	
			>100	5	100–149	34	
Prostate (n = 94)	74	25 (34%)	80–89	3	25–49	1	3 (one study explicitly stated 'no transfusion allowed')
			90–99	10	50–99	24	
			>100	4	100–149	0	
Lung (n = 89)	75	38 (51%)	80–89	4	25–49	1	5
			90–99	17	50–99	3	
			>100	4	100–149	34	

All trials that allowed for transfusion were for hemoglobin adjustment specifically (none stipulated whether transfusion was allowed for meeting platelet thresholds).

The stipulated transfusion modifiable levels were for inclusion, exclusion and general patient requirements.

Information for the above analysis was taken from the Ontario Cancer Registry on 2 December 2010. A total of 479 studies were listed at that time [101].

Of the treatment studies listed for the three disease sites reviewed, 34–51% stipulated an inclusion or exclusion requirement based on a transfusion-modifiable laboratory value (hemoglobin and/or platelet count). When a value was stipulated, the majority of studies stipulated hemoglobin levels of 90 g/l (range 80–110 g/l) and/or a platelet count of 100×10^9/l (range 50–150 $\times 10^9$/l). We analyzed the registry for studies with an albumin level requirement; however, in the cancer types selected no albumin criterion was noted. Of the studies that stipulated an entry level hemoglobin or platelet requirement, 10% stated that transfusion was acceptable and only 1% stated that no transfusion was permitted. The remaining did not explicitly state whether transfusions were or were not allowed. Of note, at our institution, the transfusion of red blood cells is recommended if the hemoglobin level is less than 70 g/l, or less than 100 g/l in the setting of symptomatic anemia (e.g., presyncope, tachycardia, shortness of breath on exertion). The most common enrolment threshold of 90 g/l would be above most hospital guidelines' trigger for prophylactic transfusions given in the absence of symptoms.

We acknowledge that reliance on trial registry information alone limits the analysis of the information presented; however, based on this snapshot, transfusion-modifiable laboratory values are often present as eligibility criteria in oncology studies.

The phenomenon of 'tweaking' patients is not restricted to oncology clinical trials. Hematology laboratory value inclusion criteria for nononcology clinical trials present similar ethical dilemmas. For example, in the randomized control trial for recombinant, activated protein C in the treatment of severe sepsis, patients with platelet counts of less than 30×10^9/l were excluded from randomization [2]. Whether platelet transfusion could be utilized to meet the criterion was not stipulated. Some intensivists have translated this enrolment criterion to mean that before and during treatment with this drug, all patients must be transfused platelets to achieve this target. In a more recent randomized trial of the same agent, but in a different patient population (acute lung injury), patients with platelet counts of $<30 \times 10^9$/l were excluded from randomization, regardless of whether the platelet count is increased after transfusion, suggesting that this issue of modifying the platelet count with transfusion was discussed by the investigators at the time of trial design [3]. Of note, a cutoff of an international normalized ratio (INR) of three was also set for this trial, but there was no stipulation as to whether plasma transfusion could be given to meet this criterion. Similarly, in a thrombolysis trial in acute stroke, patients with an elevated partial thromboplastin time, a prothrombin time greater than 15 s or a platelet count below 100×10^9/l were excluded [4]. At our institution, some clinicians do not administer thrombolysis to such patients and other clinicians administer plasma and platelets and then proceed with thrombolysis. Clearly, these ethical dilemmas do occur and extend far beyond oncology trials.

Why does tweaking occur? A nexus of conflicting & complimentary interests

Understanding how these ethical dilemmas arise and why such practice variances (as reported earlier) result, is complicated. We believe a significant contributing factor involves the tangled web of conflicting and complimentary interests that exist in the operationalization of clinical trials. Clinical trials and clinical care share many similar features and overlap in practice, yet from a regulatory and oversight perspective they are considered distinct and separate enterprises. Patients, clinicians, bioethicists and pharmaceutical sponsors approach this overlap from one of two distinct viewpoints: a 'similarity' position that perceives that the same ethical principles that govern clinical care applies to clinical trials, or a 'difference' position that sees these two settings as being very distinct and needing to be evaluated using different ethical perspectives [5]. Greater appreciation and consideration of the different perspectives of the stakeholders involved may hold the key to better understanding why tweaking patients for clinical trial or drug eligibility occurs and perhaps can lead to improved trial operation that is more easily translated into clinical practice.

■ Patient/research subject

Patients enrolling in clinical trials, particularly Phase III trials, are seeking therapeutic benefit. Altruistic motives, embedded in the desire to assist in the development of new treatments for future patients are at best held in tension with an overwhelming drive towards self preservation, or at worst, overcome by it in a younger patient dealing with an incurable disease. Therapeutic misconception may occur where the patient does not appreciate that participation in research is not the same as receiving treatment [5]. This may impede true informed consent because the patient overestimates the clinical benefit of the proposed treatment, underestimates the potential risk of harm and underappreciates the alternatives to participation in a clinical trial. As a result, the patient may be willing to accept additional treatments such as transfusion in order to gain access to participation in clinical trials offering otherwise unavailable new treatments.

> "...consideration of the different perspectives of the stakeholders involved may hold the key to better understanding why tweaking patients for clinical trial or drug eligibility occurs..."

Blood and blood-product transfusions are distinct forms of therapy with carefully prescribed applications and inherent risks that are not well understood by the general public. Presumably, hemoglobin and platelet thresholds are in place to exclude patients who may be at risk of serious cytopenias if exposed to the study treatment. The hemoglobin and platelet thresholds should be based on scientific rationale such that patients should only be excluded where there is significant concern regarding the ability of the bone marrow to tolerate the marrow-suppressive effects of the study treatment. Patients with anemia of malignancy, rather than anemia from bone marrow infiltration, should be able to tolerate the drug without significant toxicity and should not be excluded. Clearly more specific anemia criteria, rather than hemoglobin level alone, should be detailed in the inclusion/exclusion criteria. Using transfusions as a sole means of meeting clinical trial eligibility criteria poses serious risk to both the current and future patients for which the therapy is being tested. In the current patient, a transfusion to modify laboratory results could allow a patient with an inadequate bone marrow reserve into a study, potentially exposing them to greater treatment toxicity. Using higher than recommended transfusion thresholds exposes the patient to unnecessary risks that would be above and beyond what that patient would be exposed to outside of the clinical trial. In terms of future patients, the enrolment of sicker patients could impact on the internal validity of the study by documenting poor outcomes in patients that should have been excluded and throw the efficacy of the new treatment into doubt.

■ Physician/investigator

To understand why physicians might consider transfusing patients to meet eligibility criteria, it is important to explore what physicians believe is the purpose of clinical trials. Unsurprisingly, a majority of oncologists experience a tension between their dual roles as physician/patient advocate and research investigator. In 2002, Joffe and Weeks published the results of a survey that explored how oncologists viewed clinical trials [6]. The survey asked the oncologist/investigator to think about clinical trials from two perspectives: the reason why they offer a specific patient enrolment into a study; and, what they perceive to be the main purpose of the study from a societal perspective. When asked what the main reason was for enrolling individual patients into a clinical trial, medical oncologists responded accordingly: to improve to treatments for future patients (40%); ensure their patients get the most state-of-the-art treatment (43%); and to have something to offer when no standard treatments options are available (14%). When asked what they believed to be the main societal purpose of clinical trials, using the same responses, they provided the following: to improve treatments for future patients (73%); to ensure their patients get the most state-of-the-art treatment (20%); and to have something to offer when no standard treatments options are available (5%). These results suggest that many oncologists/investigators believe that clinical trials do provide benefit to the participants whether the benefit

is from offering state-of-the-art treatment or treatment that would otherwise be unavailable. In fact, there exists a sincere belief in the oncology community that clinical trials represent optimal care – "a perfect harmonization of the objectives of patient care with those of scientific advancement" [7]. This bias can impact the means used to facilitate enrolment of patients into clinical trials. If necessary to meet eligibility criteria, physicians may view transfusion as a small risk for the potential benefit of a new treatment for their patients.

"An explicit statement of whether or not transfusion is permitted to meet clinical trial eligibility should be made so as to allow appropriate interpretation and generalizability into clinical practice for future patients."

Oncologists may be more likely to offer transfusion to their patients to meet eligibility criteria if they do not believe the rationale for the criteria is reasonable. When planning clinical studies, investigators should carefully consider the reason for establishing a specific transfusion-modifiable threshold. For example, a hemoglobin threshold of 90 g/l was the most common threshold used as an eligibility criterion in our snapshot analysis of cancer clinical trials in Ontario. Is a patient with a hemoglobin of 80 g/l at higher risk than a patient with a hemoglobin of 90 g/l of having adverse effects from the study drug? Does the patient with a hemoglobin of 80 g/l have such a different prognosis from the patient with a hemoglobin of 90 g/l as to be justifiably excluded from the clinical trial? If the answer to these questions is no, then the physician may believe that modifying the value (tweaking) by whatever means (transfusion) may be valid so as to render the patient eligible either for the patient's benefit or for increased enrolment in the trial.

Part of this ethical discussion must also consider that most cancer centers or research programs receive funds for each patient enrolled in a clinical trial. Hence, the institution has economic interests in maximizing patient enrolment. Often research dollars from industry-funded trials subsidize other research performed at the hospital through the indirect funding of research personnel and infrastructure.

Lastly, the physician ordering the blood product to tweak a patient for a clinical trial may not have up to date knowledge about transfusion. They may not be aware of the life-threatening complications of transfusion, such as transfusion-related acute lung injury and bacterial contamination. Physician knowledge of the indications for transfusion and their risks has been documented to be poor [8], as has the completeness of the pretransfusion consent process, which should include a discussion about the risks, benefits and alternatives to transfusion [9]. We suspect that the use of blood products to modify laboratory numbers is seen as a 'zero-risk' maneuver by the clinician, and probably communicated to the patient as such, despite the potentially serious consequences of transfusion.

Sponsor

Well-designed and executed randomized clinical trials (RCTs) are generally acknowledged to be the most unbiased measure of efficacy for new medical treatments. RCTs rely on protocol eligibility criteria to outline patient-specific characteristics that define and ultimately limit the type of patient that can be enrolled in a trial. The determination of eligibility criteria is a valuable methodological component of RCT design to minimize bias between the control and treatment groups. Limitations on eligibility criteria typically come in the form of age, sex and laboratory value restrictions [10]. Paradoxically, inclusion and exclusion criteria may lead to uncertainties regarding the extent of generalizability of results to important subgroups of patients. Restrictive inclusion and exclusion criteria can result in choosing the 'best' patients with the greatest likelihood of having good outcomes – inferring that the more restrictive the inclusion criteria the better the drug's performance in a clinical trial. Van Spall *et al.* reported, in a systematic review of RCTs published in high-impact medical journals, that approximately 37.1% of the stated exclusion criteria were poorly justified [10]. Poorly justified criteria can result in a failure of the trial to mimic actual clinical practice and can result in decreased trial accrual and increased costs.

For the setting of transfusion modifiable criteria, there is a need for closer scrutiny of trial protocols in the design, scientific and ethical processes to ensure patient safety and generalizability of the results. As discussed previously in the 'Physician/investigator' section, the specific thresholds set should be based in scientific rationale. An explicit statement of whether or not transfusion is permitted to meet clinical trial eligibility should be made so as to allow appropriate interpretation and generalizability into clinical practice for future patients. Finally, if transfusion is permitted, guidelines for transfusion should follow best practices so as to avoid unnecessary risks to the patient.

How can we address this ethical dilemma? Conclusions & recommendations

In the current state of clinical trials, clinical investigators will encounter the ethical dilemma of modifying a laboratory value with transfusion for the sole purpose of meeting eligibility criteria. The forces that lead to this ethical dilemma may include the patient's motivation to participate, the clinician investigator's motivation to enroll patients, and a wish to gain access to

new treatments or treatments that might otherwise be unavailable. The sponsor may enable this practice by setting eligibility criteria that the clinician investigator does not believe are justifiable and by not explicitly stating the role of transfusion in modifying eligibility criteria. This, in turn, can lead to poor generalizability of the results of the study to clinical practice and more importantly, risks to patient safety. We suggest that close attention to the decision-making process that outlines transfusion modifiable criteria is required by all parties involved. To advance this ideal, the following recommendations are proposed:

- Research ethic boards and institutional review boards (REB/IRB) need to be aware of this issue and incorporate these considerations into their review of protocols;
- Transfusion modifiable eligibility criteria should be associated with either scientific inference or patient safety, and must include a scientific basis;
- Every reasonable effort should be made to minimize exclusions of specific-patient populations when such patients would likely form a group to which the results would be generalized [10];
- Advocate for broader eligibility criteria, wherein physicians and patients should jointly make an informed decision about patient entry into the trial. As with all medical decisions, this decision should take into account the patient's current medical condition, past medical history, and any other relevant considerations [11];
- The clinical investigators should investigate all possible alternatives to correcting underlying laboratory values through treatments other than transfusion;
- Protocols detailing transfusion-modifiable eligibility criteria should address the role of transfusions;
- When transfusion is permitted, transfusion protocols should be in line with the most recent evidence based guidelines and best practices;
- The practice of using transfusions to meet eligibility requirements must be included in the scientific reporting of study results.

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Website

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