Adequacy of Published Oncology Randomized Controlled Trials to Provide Therapeutic Details Needed for Clinical Application

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Background
Randomized controlled trials (RCTs) improve clinical care through evidence-based results. Guidelines exist for RCT result reporting, but specific details of therapeutic administration promote clinical application and reproduction of the trial design. We assess the reporting methodology in RCTs published in major oncology journals.

Methods
Ten essential elements of RCT reporting were identified and included drug name, dose, route, cycle length, maximum number of cycles, premedication, growth factor support, patient monitoring parameters, and dosing adjustments for hematologic and organ-specific toxicity. All therapy-based oncology RCTs published between 2005 and 2008 in the New England Journal of Medicine (NEJM), Journal of Clinical Oncology (JCO), Journal of the National Cancer Institute (JNCI), Blood, and Cancer were analyzed for inclusion of these 10 elements.

Results
Of 339 identified articles, 262 were included in the final analysis (165 from JCO, 31 from NEJM, 27 from Cancer, 20 from JNCI, and 19 from Blood). Premedication, growth factor support, and dose adjustments for toxicities were each reported less than half of the time. Only 30 articles (11%) met the main objective of complete data reporting (ie, all 10 essential elements) and was highest in JNCI (5/20; 25%), followed by Cancer (5/27; 18%), JCO (18/165; 11%), Blood (1/19; 5%), and NEJM (1/31; 3%). The presence of an online appendix did not substantially improve complete reporting.

Conclusions
RCTs published in major oncology journals do not consistently report essential therapeutic details necessary for translation of the trial findings to clinical practice. Potential solutions to improve reporting include modification of submission guidelines, use of online appendices, and providing open access to trial protocols.

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The publication of randomized controlled trials (RCTs) enables dissemination of the findings of clinical investigations that aim to improve clinical practice. These documents serve as sources of information that medical providers seek to apply evidence-based medicine to patient care (1). RCTs are precisely regimented, and their protocols provide clear instructions regarding drug administration, patient monitoring, toxicity management, and therapeutic dose modifications. These instructions should be capable of reproduction once the trial results are published to enable clinicians to replicate study design and methodology and achieve similar outcomes. Ideally, the trial details that are disclosed should be readily accessible, easy to interpret, and immediately transferable to the clinical setting (2). The International Committee of Medical Journal Editors has established reporting guidelines that are applicable to the preparation of all RCT manuscripts, and most major oncology journals reference these guidelines in their author submission standards. Despite these standards, there is no set policy or accepted format for reporting details associated with drug administration or patient monitoring (2). Thus, published reports of investigations of chemotherapies and/or biologic therapies often lack some details needed for safe and effective translation to clinical application.

Oncology care delivery is frequently evaluated to develop approaches that limit errors and improve quality performance (3). The emergence of standardized practice, such as the adoption of clinical practice guidelines and electronic chemotherapy forms, promotes consistency across patient care (4,5). Drug-related errors in oncology can have fatal consequences (6,7). As a result, multidisciplinary task forces have been developed to evaluate weaknesses in health-care systems that create an avenue for potential errors (7). Nearly one-third of all medication-related errors occur during administration and are preventable if the elements necessary to deliver drugs are provided in a clear concise manner (8).

Because of our experience in clinical practice, we hypothesized that many RCTs published in major oncology journals are deficient in reporting important therapeutic details. This study was developed to assess the degree to which published manuscripts in top-tier oncology journals provide sufficient details regarding therapy administration, patient monitoring, and supportive care provisions for safe and effective clinical application of the study design.
Table 1. Elements required to adequately deliver oncology therapeutics reported in randomized controlled trials

| Essential elements                                      |
|--------------------------------------------------------|
| Drug name                                              |
| Dose administered                                      |
| Route of administration                                |
| Cycle length                                           |
| Maximum number of cycles                                |
| Premedication (supportive therapy)                      |
| Growth factor support                                   |
| Patient monitoring parameters                           |
| Dosage adjustment for hematologic toxicity              |
| Dosage adjustment for organ-specific toxicity           |
| Other desired elements (not included in analysis)       |
| Order of drug administration in multiple drug regimens  |
| Drug infusion rate                                      |
| Preparation of chemotherapy (diluents)                  |

Methods

A diverse group of clinical oncology providers was randomly selected, which included six academic medical oncologists, five oncology clinical pharmacists, six oncology fellows, and four midlevel providers (advanced registered nurse practitioners or physician assistants). Participants were instructed to generate an ad hoc list of details necessary for clinical application of any oncology drug therapy. Survey results were collected and collated (Table 1). The 10 most commonly requested details were defined as the essential elements and included drug name; dose; route; cycle length; maximum number of cycles; premedication with steroids, antiemetics, and/or antihistamines before therapy administration; myeloid growth factor support use; monitoring parameters for response to treatment and development of toxicities; and dosage adjustments for hematologic and organ-specific toxicities. Other desirable elements that did not reach consensus were also listed (Table 1) but are not included in this analysis.

A PubMed search was performed on December 1, 2008, using the key words “chemotherapy” and “randomized controlled trials.” Results were limited to articles published between January 1, 2005, and November 30, 2008, in the *Journal of Clinical Oncology* (*JCO*), the *New England Journal of Medicine* (*NEJM*), the *Journal of the National Cancer Institute* (*JNCI*), *Blood*, and *Cancer*. Only phase III RCTs were chosen for review. Meta-analyses and review articles were excluded. Eligible articles were analyzed for inclusion of these 10 elements either in the printed manuscript or through associated online appendices, when available. Each article was assigned a point for each element reported with potential scores ranging from 0 to 10. A score of 10 defined complete data reporting.

The primary objective of the study was to determine the incidence of complete data reporting. Secondary objectives included determining differences in reporting of each element, differences in reporting between journals, and the potential impact of an online appendix. Calculations were conducted using Minitab (Minitab, Inc, State College, PA).

Results

A total of 339 unique articles were identified, of which 77 were reviews, meta-analyses, or phase I or II trials and were thus not included. Therefore, 262 phase III RCTs were included in the final analysis (165 from *JCO*; 31 from *NEJM*; 27 from *Cancer*; 20 from *JNCI*; and 19 from *Blood*). The median number of elements reported per manuscript was 7.3 out of 10 (range 2–10). There was not a substantial difference in the median number of elements reported between journals. Elements reported greater than 90% of the time included drug name, dose, cycle length, and maximum number of cycles (Table 2). Premedication, growth factor support, and dosage adjustments for hematologic and organ-specific toxicity were the least reported elements and were included 43%, 40%, 41%, and 42% of the time, respectively.

A total of 30 articles (11%) met the primary objective of reporting all 10 elements. Complete data reporting was highest in *JNCI* (5/20 articles; 25%), followed by *Cancer* (5/27; 18%), *JCO* (18/165; 11%), *Blood* (1/19; 5%), and *NEJM* (1/31; 3%) (Figure 1). Four of the five analyzed journals (*NEJM, JCO, JNCI, and Blood*) support an online appendix for supplemental material; however, among the 262 articles reviewed, only five articles (three in *JCO* and two in *NEJM*) made reference to this tool and used this resource. One of these five articles (in the *JCO*) achieved complete data reporting using the information supplied in the appendix; however, use of the online appendix did not substantially improve the reporting scores of the other four articles. The supplemental material included premedication and dosage modifications.

Discussion

To our knowledge, this is the first study to systematically evaluate the reporting of therapeutic details necessary for the clinical application of findings from RCTs in top-tier oncology journals. We specifically focused on a limited group of article types (phase III RCTs) and journals. The selection of RCTs was to identify those

**CONTEXT AND CAVEATS**

**Prior knowledge**

Guidelines exist for reporting of randomized controlled trials (RCTs), but in practice, authors often omit details needed for their clinical application.

**Study design**

The authors identified 10 elements necessary for the reproduction of trial conditions in the clinic and surveyed all RCTs of cancer therapies published from 2005 to 2008 in five leading cancer journals for the inclusion of these elements.

**Contribution**

Only 11% of the publications surveyed adequately reported all 10 elements.

**Implications**

The authors encourage the oncology community to facilitate improved reporting of RCTs.

**Limitations**

The list of 10 essential elements was selected by a small group of clinicians, and it is possible that additional important elements were overlooked.

*From the Editors*
studies which have the most potential for direct clinical application, whereas the journal selections were based on publication impact factor and relevance to clinical practice. Analysis of 262 reports of phase III RCTs that investigated the effectiveness of various chemotherapies and/or biologic therapies revealed insufficient reporting of data considered to be essential for clinical application. Overall, only 11% of these articles demonstrated complete data reporting as defined by inclusion of all 10 essential elements. The median number of elements reported was 7.3. However, supportive care use, patient monitoring, and dosing modifications for organ-specific dysfunction or hematologic toxicity were uniformly reported less than half of the time.

These essential elements were determined by ad hoc surveys of clinical oncology providers with various levels of experience within a large academic cancer center. As such, perspectives of community practitioners were not fully represented. The “top 10” list was derived from a variety of providers with different levels of training, experience, and clinical knowledge. It represents elements that are felt, in total, to be relevant to the clinical application of a study drug. However, it is possible that some additional elements might be missed or underrepresented because those surveyed came from an academic practice environment.

Within each article, every attempt was made to consistently score each element reported. Several articles in our analysis reported on therapeutic agents for which certain elements (ie, drug route or premedication) were either assumed or deemed not to be applicable. Specifically, these articles reported results of oral hormonal-based therapies for which only one administration route is available and premedication is not routinely used. These represented only 15 (6%) of the manuscripts reviewed. Nevertheless, the article was considered deficient in reporting of these elements if not explicitly addressed. We believe that these elements should be consistently included, regardless of assumed clinical knowledge, because of the rapidly changing treatment options for cancer therapy, the large number of novel agents that come into clinical practice via RCTs, and the heterogeneity of oncology provider experiences.

In recent decades, clinical trial data reporting guidelines have been developed, with the most widely recognized being the Consolidated Standards of Reporting Trials (CONSORT) guidelines (9). These have undergone revision to provide authors a detailed checklist and flow diagram to promote adequate data reporting (9,10). Despite having such guidelines in place, transparency in reporting and justification for exclusion criteria has been called for (11). Given that additional details inherent to oncology-based trials and clinical care are beyond those recommended by the CONSORT guidelines, individual journals are left to provide oversight of such reporting details. Yet, the author submission guidelines specific to oncology journals do not provide instruction on standard reporting of the complexities of chemotherapy administration or oncology patient monitoring (12–16). Development of standard manuscript submission guidelines for oncology RCTs will help to improve the consistent reporting of trial methods and monitoring. Increased toxicities and reduced efficacy of new agents when evaluated in phase IV or postapproval clinical adverse event reporting may be partially explained by a lack of detailed information in the licensing trial methodology. Thus, better RCT reporting would help to promote safe and effective clinical application of oncology therapeutics.

Because of publishers’ word count limitations, most studies appropriately focus on reporting scientific data to support the trial endpoints and conclusions; however, online appendices can provide additional space for information not otherwise contained in the primary document because they are not under word count constraints. Four of the five evaluated journals currently provide links to an online appendix or supplementary material section. Of the 262 articles reviewed from 2005 to 2008, articles in only two journals

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**Table 2. Percentage of therapeutic elements reported in oncology randomized controlled trials**

| Elements | Blood (n = 19), n (%) | Cancer (n = 27), n (%) | JCO (n = 165), n (%) | JNCI (n = 20), n (%) | NEJM (n = 31), n (%) | Total (n = 262), n (%) |
|----------|----------------------|-----------------------|---------------------|---------------------|----------------------|----------------------|
| Drug name | 19 (100)             | 27 (100)              | 165 (100)           | 20 (100)            | 31 (100)             | 262 (100)            |
| Dose     | 19 (100)             | 26 (96)               | 164 (99)            | 20 (100)            | 30 (97)              | 257 (98)             |
| Route    | 18 (95)              | 23 (85)               | 139 (84)            | 14 (70)             | 26 (84)              | 220 (84)             |
| Cycle length | 19 (100)           | 27 (100)              | 164 (99)            | 20 (100)            | 30 (97)              | 260 (99)             |
| Maximum cycles | 19 (100)         | 25 (93)               | 155 (94)            | 20 (100)            | 30 (97)              | 249 (95)             |
| Premedication | 4 (21)            | 11 (41)               | 73 (44)             | 10 (50)             | 16 (52)              | 113 (43)             |
| Growth factor support | 12 (63)          | 12 (44)               | 60 (36)             | 10 (50)             | 11 (35)              | 105 (40)             |
| Monitoring parameters | 14 (74)       | 20 (74)               | 144 (87)            | 20 (100)            | 28 (90)              | 226 (86)             |
| Dose adjustments for | |                     |                     |                     |                      |                     |
| Heme toxicity | 8 (42)            | 10 (37)               | 68 (41)             | 12 (60)             | 11 (35)              | 108 (41)             |
| Organ dysfunction | 6 (31)          | 10 (37)               | 70 (42)             | 13 (65)             | 11 (35)              | 110 (42)             |
| Total % reported elements | 73             | 71                    | 73                  | 80                  | 72                   | 73                   |

* JCO = Journal of Clinical Oncology; JNCI = Journal of the National Cancer Institute; NEJM = New England Journal of Medicine.
(NEJM and JCO) had used this resource. These appendices were easily accessible and provided additional details of interest to this study but only helped to complete the reporting of all 10 essential elements in one of five articles. Expanded use of online appendices for such details should be considered as one possible solution to improve RCT reporting (Table 3). Because all RCTs are conducted through stringent protocols that clearly outline the exact delivery of every therapy and the monitoring of every patient, many manuscripts simply refer to the original trial protocol for additional information regarding methodology details. However, these documents are rarely open source and are not readily accessible to most practicing clinicians who did not participate in the original conduct of the study. Therefore, another solution might be to link published RCTs to open access trial protocols as a resource for clinicians. Additionally, journals, professional societies, and/or clinical guideline organizations can define a set of essential elements and require their consistent reporting in oncology therapeutic study results (Table 3).

In conclusion, published RCTs often do not consistently report important details required for the clinical application of oncology therapeutics and for reproduction of the trial design in the clinical setting. Although stringent scientific guidelines exist for reporting RCT results, there are no standards for reporting how chemotherapy or biological therapeutics should be administered, even in top-tier oncology journals. Insufficient reporting can create clinically relevant challenges in delivering safe and effective oncology care consistent with the objectives of scientific advancement. Potential solutions range from expansion of the standard manuscript submission guidelines to open access of clinical trial protocols. Standard editorial policies should be modified to improve the consistent reporting of methodology that is not only scientifically sound but also safe and clinically transferable.

References
1. Wolff A, Desch C. Clinical practice guidelines in oncology: translating evidence into practice (and back). J Oncol Pract. 2005;1(4):160–161.
2. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. http://www.icmje.org. Accessed March 14, 2009.
3. McNiff K. The Quality Oncology Practice Initiative. J Oncol Pract. 2006;2(1):26–30.
4. Dumasia L, Harris E, Drellichman A. Quality performance improvement with the implementation of standard chemotherapy order forms. J Oncol Pract. 2006;2(3):104–107.
5. Davis D, Taylor-Vaay A. Translating guidelines into practice: a systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. Can Med Assoc J. 1997;157(4):408–416.
6. Cohen MR, Anderson RW, Atilio RM, et al. Preventing medication errors in cancer chemotherapy. Am J Health Syst Pharm. 1996;53(7):737–746.
7. Goldspiel BR, DeChristoforo R, Daniels CE. A continuous-improvement approach for reducing the number of chemotherapy-related medication errors. Am J Health Syst Pharm. 2000;57(suppl 4):S4–S9.
8. Shane R. Current status of administration of medicines. Am J Health Syst Pharm. 2009;66(5)(suppl 3):S42–S48.
9. Moher D, Schulz KF, Altman DG, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 2005;1(1);40–45.
10. Rennie D. CONSORT-revised improving the reporting of randomized trials. JAMA. 2001;285(15):2006–2007.
11. Van Spall HG, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals. JAMA. 2007;297(11):1213–1240.
12. Blood: Information for Authors: Style Guide. http://bloodjournal.hematologylibrary.org/misc/flora.dtd. Accessed March 14, 2009.
13. Cancer: Instructions for Authors. http://www3.interscience.wiley.com/homepages/28741/cancer_instrux.pdf. Accessed March 14, 2009.
14. Journal of Clinical Oncology: Manuscript Preparation Guidelines. http://jco.ascopubs.org/ftp/prepareguide.dtd. Accessed March 14, 2009.
15. Journal of the National Cancer Institute: Instructions to Authors. http://www .oxfordjournals.org/our_journals/jnci/for_authors/index.html. Accessed March 14, 2009.
16. The New England Journal of Medicine: Author Center Help: Instructions for Submitting a New Manuscript. http://authors.nejm.org/help/NewMs.asp. Accessed March 14, 2009.

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