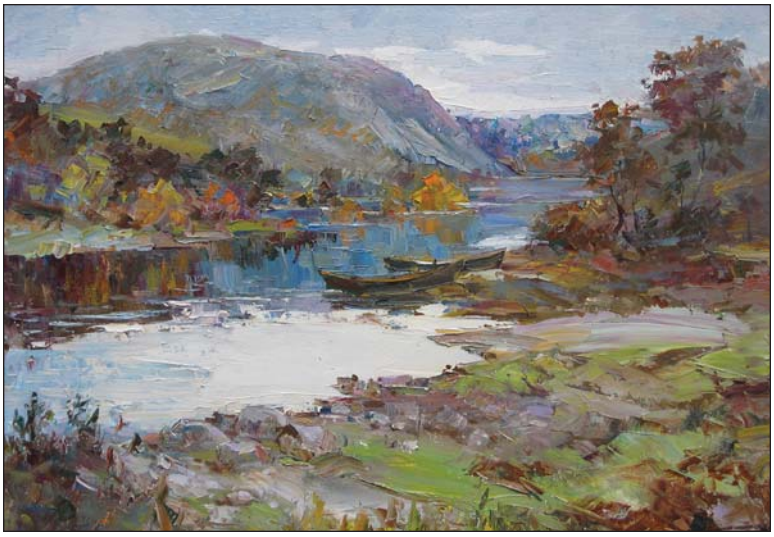

Alexey Bobylev. *Creek of Inspiration,* 2004. Oil on canvas, 50 × 70 cm. Courtesy of the St. Petersburg Art Salon, Russia.

It is more difficult to establish a true treatment effect in a rare versus a common disease.

Evidence-Based Medicine for Rare Diseases: Implications for Data Interpretation and Clinical Trial Design

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Background: *The randomized, controlled trial (RCT) is the "gold standard" for establishing the effect of any intervention. This approach, however, is often not feasible with rare diseases such as cutaneous T-cell lymphoma.*
Methods: *We review the principles of evidence-based medicine to see which are particularly pertinent to the study of rare diseases.*
Results: *When an RCT is not feasible, attention is given to determining all the available prior data. Evaluation of the new data and the historic base requires attention to biases, but can allow estimation of a "true" study result.*
Conclusions: *Even when an RCT cannot be performed because of insufficient cases, utilization of evidence-based methodology can help minimize bias and maximize the truth of observed new data.*

Introduction

Physicians require reliable information to understand, diagnose, treat, or establish the prognosis for any disease.[1,2] However, the methods for acquiring and interpreting relevant evidence in clinical research is not universal and well defined. The methods that can be used for assimilating relevant clinical information for rational clinical decision making according to the principles of evidence-based medicine are presented in this article. Although the issues are relevant to all types of diseases, we have focused on the application of these principles in the study of rare diseases. In this paper, the treatment aspects of rare diseases such as peripheral T- and NK-cell lymphoma/leukemia are presented as examples.

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Abbreviations used in this paper: RCT = randomized, controlled trial.

By their very nature, it is often difficult to design clinical trials of any type for a rare disease due to the infrequency of the incidence of the disease. A rare disease is defined as a condition or disease affecting fewer than 200,000 individuals in the United States.[3]

About 6,000 such diseases have been identified, affecting an estimated 25 million Americans. In consideration of the issue related to treatment, it is important to bear in mind that the question of therapeutics is always an exercise in comparison. Therefore, the efficacy of any intervention for a rare disease may be difficult to establish due to an insufficient number of patients. This is particularly true since a large majority of the patients will not be eligible for the trials (discussed later). However, this does not preclude utilizing all the associated information available from different sources, which is the underlying principle of evidence-based medicine.

Matching Clinical Trial Design With Underlying Uncertainties

The purpose of science and clinical research is to address the existing uncertainties (in our case, the effects of various treatments that we may wish to test).[2,4-6] Clinical uncertainties come in different shades and forms, and not all clinical trials methods are equally suitable to address all types of uncertainties.[7,8] Figure shows taxonomy of clinical uncertainties. As illustrated, the choice of scientific method should match the underlying level of uncertainty. The central question is determining if the effects are real and reproducible. Therefore, before providing an answer regarding which clinical trial design should be used to address certain types of uncertainties, we briefly review the factors that can affect the direction and strength of treatment effects.

Interpretation of Research Findings

When a study is completed, there are three possible explanations for the results of a study: (1) the findings are true, (2) the results are due to a random variation (the chance effect), or (3) the findings are due to the effect of systematic error (bias).[9,10] Bias is defined as systematic misrepresentation of the estimated treatment effect due to inadequacies in the design, conduct, or analysis of the trial.[9,10] Random error is defined as the effect of play of chance on the results of the study.[9,10]

The methodological quality of a trial should always be considered when analyzing study results because evidence has shown that results from poorly conducted research can lead to flawed decision making at all levels (ie, at the level of patients, physicians, or policy makers).[11] Hence, in order to preserve the quality of the trial and to make a clear-cut distinction if the results obtained from the study are indeed true or not, bias (systematic error) and random error should be minimized. Table 1 illustrates the most important methodological features that should be taken into account in generating and interpreting clinical research. This table also lists the best known methods for control of bias and random error.[12-18]

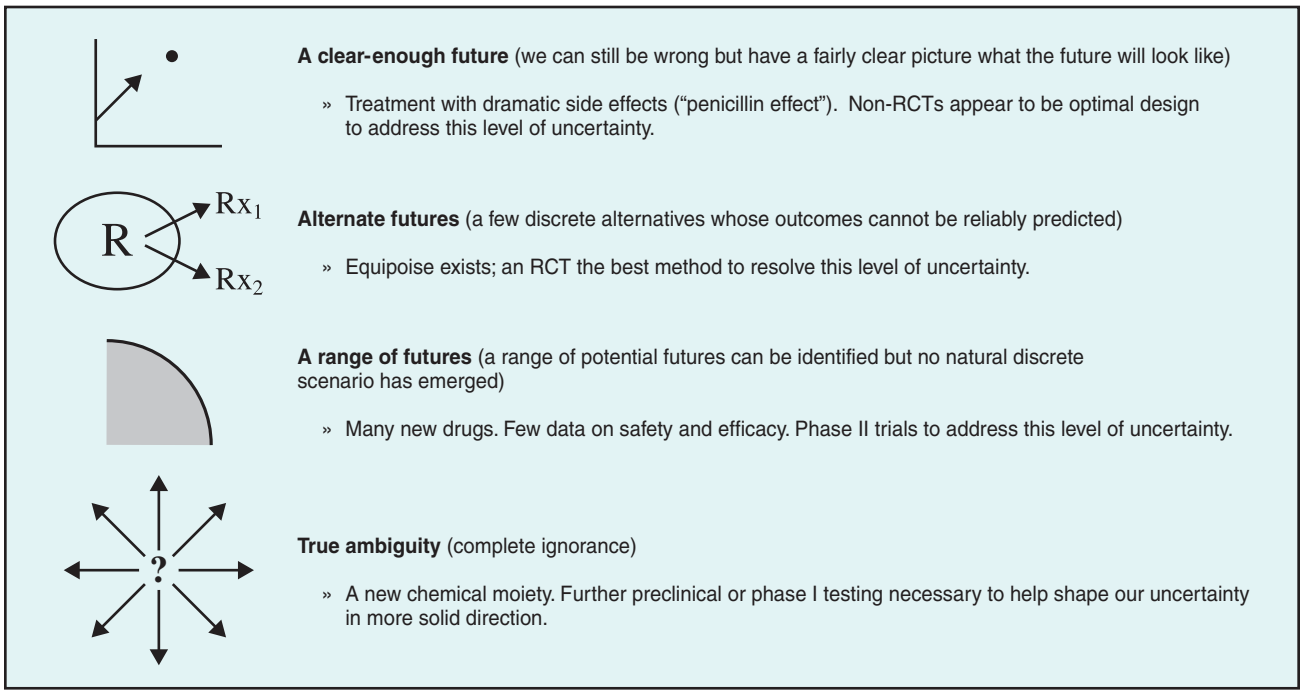

Figure. — Taxonomy of clinical uncertainties: matching clinical trial design with underlying uncertainties about treatment effects. Modified from Courtney H, Kirkland J, Viguerie P. Strategy under uncertainty. *Harv Bus Rev.* 1997;75:66-79. Reprinted with permission by Harvard Business School Publishing. Please also see Reference 8.

A large body of evidence exists showing that the effect of the various biases or play of chance might distort the direction of the interventions that were studied.[11,19-21] As a rule, these biases are typically more pronounced in observational and nonrandomized studies than in randomized, controlled trials (RCTs).[22] Because randomization can effectively eliminate biases in comparisons of treatments, RCTs are seen as a more superior method of clinical inquiry.[20]

It is also useful to distinguish between internal validity, ie, the extent to which a trial provides valid information about conditions and patients it studied, and external validity, ie, the extent to which the study findings can be applied (generalized) to other clinical setting that are different from those in which the results were originally generated. The studies with high internal and external validity are called high-quality studies.[23,24] These are studies in which we have high confidence that an estimate of the effect is correct.[23,24] It is important to note that if the study has poor internal validity, then the generalizability of such a study is worthless. Historical data from clinical studies treating aggressive peripheral T-cell non-Hodgkin's lymphoma (NHL) serve as an example of poor internal validity.[25-27] Peripheral T-cell lymphoma is a heterogeneous group of lymphoid disorders that include entities with a poor prognosis (eg, peripheral T-cell NHL with a 5-year overall survival rate of 25%) as well as entities with a good prognosis (eg, anaplastic lymphoma kinase-1 positive (ALK-1+) anaplastic large T-cell NHL, with a 5-year overall survival rate of 80%).[28] A comparison of the entire group of aggressive T-cell lymphoma with large B-cell NHL led to the erroneous conclusion that there is no difference in the prognosis of aggressive T- and B-cell lymphoma.[25,26] Finally, we should note that even if a given study is high quality, it rarely, in isolation, provides sufficient credence for us to accept it. In fact, the most credible method to generate reliable evidence is by conducting a well-designed and adequately powered clinical trial informed by the systematic review of the totality of existing research evidence.[2,29]

Table 1. — Factors That Affect the Strength and Direction of Treatment Effects*

Bias/Random Error	Factors	Methods to Control
Selection Bias (Are we comparing like with like?)	Use of historical controls Improperly defined inclusion/exclusion criteria Selection of treatment according to prognostic features, etc (overall can obscure up to 40%-70% of true treatment effect)[10,12,13]	Adequate allocation concealment Randomization If randomization not possible, prospective enrollment of consecutive series of patients (with alteration of treatment assignment, eg, even vs odd days etc) is the next best method
Performance Bias (Are we controlling for co-interventions/ contaminations)	Use of co-intervention(s) (apart from the main treatment that is tested) administered in non-uniform way (eg, due to differences in center or physicians practices) (can obscure up to 50% of true treatment effect)[14]	Adequate allocation concealment Adequate blinding or masking Standardization of care among participating centers/physician
Attrition Bias (Are we accounting for drop-outs?)	Due to missing data from losses to follow up or drop-outs.(depending on the extent of drop-outs, true treatment effects can be completely overridden)[15]	Intention-to-treat analysis (explicit account of all withdrawals and drop-outs (if it is >10%–20%, view the results of a study with extreme caution)
Detection Bias (Are we controlling for observer bias?)	Inadequacies in outcome assessment (eg, those who assessed outcomes were potentially biased because they knew the results of the study at the time of outcome assessment, this can obscure up to 15% of true treatment effect)[10,13]	Prevent inadequacies in outcome assessment (eg, "blinding" of those who will assess the outcome from the result of the study) Standardized assessment (eg, RECIST criteria in evaluation of tumor responses)[16]
Publication Bias (Are the results of the study due to selective-citation bias?)	Published literature reporting the result of a trial is biased in favor of positive or promising outcomes due to analysis of selective set of the studies[17]	Registration of clinical trials Patient registry
Random Error (Are we controlling play of chance?)	Statistical measurement variation; increased if the study is under-powered Depending on trial size, true treatment effects dramatically vary in all directions[18]	Adequate sample size Planning of realistic and clinically meaningful differences between treatments Reporting needs to be accompanied with additional measures of precision, such as, standard error or confidence limits

* This is not an exhaustive list of the potential causes that may provide false conclusions. The biases can be introduced at the level of planning, conduct, analysis, and dissemination.

Table 2. — Feasibility of Conducting RCTs in Rare Diseases: Sample Size Calculations

Disease	Baseline Survival on the Current-Standard Treatments	Hypothesized (expected) Improvement on a New Treatment (realistic scenario, decrease in relative risk of death by 20%; hazard ratio = 0.8) (sample size) (assumed 3-yr accrual + 2-yr follow-up; 10% lost to follow-up)	Hypothesized (expected) Improvement on a New Treatment (overoptimistic scenario, decrease in relative risk of death by 50%; hazard ratio = 0.5) (sample size) (assumed 3-yr accrual + 2-yr follow-up; 10% lost to follow-up)	Prevalence (total number of patients available in the United States)
Indolent T-cell LGL leukemia	Median survival >10 yrs	3,380	439	160 patients/yr
Anaplastic large T-cell non-Hodgkin's lymphoma (ALCL)	80% (5 year survival, ALK+)	5,050	662	1,800 patients/yr
Peripheral T-cell lymphoma, unspecified	25% (5-yr survival)	1,143	140	4,000 patients/yr

Randomized Trials and Rare Diseases

Despite the unquestionable desire to obtain answers related to any intervention from RCTs, it is sometimes not feasible to conduct a sufficiently large RCT.[30] For instance, the availability of few patients across the globe due to the rarity of a disease makes it logistically difficult to conduct an RCT. The nonavailability of a sufficient number of patients with rare diseases is illustrated by an RCT conducted by Gallin et al[31] to test itraconazole for the prevention of severe fungal infection in children and adults with chronic granulomatous disease. This paper demonstrates the difficulties in performing RCTs in rare diseases. The investigators eventually succeeded in enrolling a specified number of patients (n = 39) but required 10 years to do so.[31] Hence, it is not surprising that clinical questions are more easily answered when the disease is fairly common and the event of interest has a high probability of occurring.[30] The feasibility criterion is one of the practical barriers to undertaking RCTs in rare diseases.

Another example that can be cited here of relevance to this issue of *Cancer Control* is T-cell and natural killer-cell lymphoma. These also belong to the group of rare diseases, with only about 7,000 new cases diagnosed in the United States annually.[32] Table 2 provides an example of sample size calculations for testing of treatments for several T-cell malignancies. Given the fact that only about 3% to 5% of patients with cancer actually enroll in clinical trials, it is logistically difficult to conduct an RCT for this disease.[33]

When Are Randomized Trials Not Needed?

Many new treatments are introduced in medicine without the need to be formally tested in RCTs. Examples include the use of penicillin, insulin, blood transfusions, and vitamin B12.[34] In these circumstances, the effects of these interventions were considered large enough to override the combined effects of bias and random errors on the study's findings. When the effects of treatments are dramatic and recognizable, an RCT might not be needed to demonstrate the efficacy of an intervention. However, questions remain: how large should the treatment effect be before it can be considered to have demonstrated self-evident efficacy that most observers would agree about the truthfulness of the reported findings? Little work has been done on this question. Some researchers have suggested a psychometric "10× rule," ie, when differences in the outcomes between two competing interventions exceed a relative risk of 10, the treatment effect can be considered large enough.[35,36] Recent work by Glasziou et al[36] aptly summarizes this issue, suggesting that if the ratio of treatment effects between two alternative therapies >10, then the treatment effect is likely to be real. Table 3 summarizes scenarios when an RCT may not be needed.

Application of Principles of Evidence-Based Medicine in Rare Diseases

Regardless of whether a disease is rare or common, it is important to consider the totality of the research evidence in order to determine true findings vs false findings. This is one of the underlying principles of evidence-based medicine.[2] In other words, both clinical trial design and interpretation of data should rely on the methodology of systematic review.[19,37] Systematic review refers to the application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic.[19,37] Meta-analysis may be, but is not necessarily, used as a part of this process. Meta-analysis represents the statistical synthesis of the data from separate but similar (ie, comparable) studies, leading to a quantitative summary of the pooled results.[19] The use of systematic review is an optimal way to avoid selective citations as the basis for the best

possible clinical trial design. Designing trials based on selective citations can lead to detrimental outcomes for the patients.[38] Similarly, systematic evaluation of the totality of evidence on benefits and harms forms the basis for rational medical decision making.[2,39]

The importance of systematic review cannot be better summarized and explained than in the title of a research paper by Clarke[40]: "Doing New Research? Don't Forget the Old." This means that conducting a systematic review before undertaking a new research provides all the evidence in its entirety regarding what is known and also what is not known. Therefore, a well-done systematic review provides the totality of the knowledge on any topic, which in turn will guide the allotment (or not) of vital resources to the research needs. Additionally, it answers the question of whether research is indeed required (or not) and ensures ethical conduct of the trial via the fact that the patients will be offered enrollment based on the best information available.

It is also important to acknowledge the existing uncertainty related to competing treatments before designing and conducting a clinical trial and to articulate those uncertainties[2,4,8,41] that are credibly linked to our estimates of the treatment effect. The taxonomy of uncertainties adopted after Courtney et al[42] effectively demonstrates the four possible scenarios in clinical research (Figure).[8,42]

In the first scenario, when the treatment effect is large and clear-cut, proverbially visible even to a blind eye, then an RCT is not required and clearly would be unethical to demonstrate its efficacy. The introduction of penicillin and insulin serve as examples for situations when an RCT is not needed due to large treatment effects.[34,36] For researchers of rare diseases, this means they would focus only on discoveries of breakthrough interventions, which is not likely to occur during most researchers' lifetimes.

In the second scenario, when an alternative treatment is clearly formulated and it is predicted that there is about equal probability of one regimen being superior to the other, an RCT is the optimal method to establish the superiority of one treatment over another. RCTs are considered ethically and scientifically justified if we are substantially uncertain which of the competing treatment alternatives is more beneficial to the patients.[2,4,43,44] This requirement is known in the literature as equipoise, uncertainty or indifference principle.[2,4,8,41,43,44] For rare-disease researchers, this means that they need to clearly articulate uncertainties related to competing treatment alternatives. For example, if they believe that there are two treatments, A and B, about whose relative effects they are equally uncertain, then a serious thought to pooling resources to organize an RCT would be the best design to address this question. However, if an RCT is clearly not feasible, then a quasi-RCT with alternative assignment of prospectively enrolled patients, with clear-cut predefined eligibility criteria, might still be acceptable. In other words, the intervention should

Table 3. — Scenarios in Which RCTs May Be Unnecessary

Scenario	Is RCT Necessary?
When the treatment effect is dramatically large (eg, meeting Sackett's "all or none" criterion, which is met when for example all patients died before the [intervention] became available, but some now survive on it; or when some patients died before the [intervention] became available, but none now die on it) or High control event rate (bad outcome of disease if untreated) with dramatic benefit of treatment (high relative risk reduction), and acceptable side effects of treatment (high/very high number need to harm), and convincing physiopathological basis	No
When the outcome is rare When the outcome happens far in the future and long follow-ups are required When randomization could reduce effectiveness	Logistically not feasible or Inappropriate
Lack of equipoise	No or ethically impossible/inappropriate
No alternative treatment	No
Large treatment effect ("10× rule")	Data from non-RCTs can be trusted if the ratio of treatment effects between two alternative therapies >10; under these circumstances, large treatment effects most likely override any effects from bias and random error that's obviating need for RCTs

Data from Djulbegovic B. Non-randomized trials that changed medical practice. Available at: http://www.hsc.usf.edu/~bdjulbeg/oncology/NON-RCT-practice-change.htm.

be assigned in the trial by means of quasi-random manner — for example, allocation by date of birth. However, compared to an RCT, results from a quasi-RCT are more prone to selection bias. Ideally, outcomes of interest should be patient-related (ie, survival, disease-free survival, quality of life). However, if credible basic science has proven an excellent correlation between surrogate markers and patient-related outcomes, then surrogate outcomes may become equally acceptable.

Since none of these solutions is ideal, a rationale for the trial design should be transparent and explicitly laid out. As discussed above, the trial design should always be guided by a preceding systematic review. Another alternative method suggested in the literature to study treatment comparisons in rare diseases is to employ Bayesian statistical design.[30] According to this method, if data from prior smaller studies are available, they may be gainfully quantified in forming a prior probability distribution and combined with the current trial data to provide the posterior distribution based on which conclusions may be drawn.[30,45,46] The key to this design is credible data on priors. This can best be accomplished by creating a registry of prospectively enrolled consecutive patients with clear inclusion criteria. Of utmost importance for creating a registry of rare diseases is the need to capture most, if not all, patients who meet clear-cut eligibility criteria. Registries that enroll a minority of patients will be plagued by selection bias (Table 1). In addition to informing the design of a particular trial by creating a registry, investigators can also establish the annual incidence (the number of new cases per year in a defined population) and prevalence (the total number of cases in a defined population) and obtain real-world data on outcomes (eg, mortality, and event-free survival). If there is a relative homogeneity in treatment and population, the pattern changes over time can lead the investigators to postulate if disease outcomes are affected with a particular treatment. This information could result in the development of testable hypotheses regarding disease treatments.

In the third scenario, when a range of potentially effective treatments are identified but no clear picture about a single treatment has materialized, phase II trials are typically conducted to better delineate safety and efficacy of available treatment alternatives. Researchers of rare diseases typically use this type of design to study new treatment alternatives as described in reports dealing with management of mycosis fungoides and diseases of large granular lymphocytes in this issue of *Cancer Control*.

The fourth and last scenario of uncertainty is associated with lack of knowledge about the treatment effects. This might arise when the efficacy or safety of an intervention is unknown, as typically happens when new chemical molecules are brought from animal to human studies. Although we can be uncertain about the value of a particular intervention, the state of existing knowledge does not allow commitment to any of the potential treatment options. Therefore, in the context of human clinical research, uncertainty (about the specific treatment choice) virtually does not exist. Further research such as preclinical or phase I testing is necessary to help shape our uncertainty in a more solid direction prior to undertaking additional investigations in humans.[2,8]

Conclusions

The goal of research remains unchanged for common and rare diseases: deciphering if our interventions are truly effective. RCTs are always desirable to answer the uncertainties related to a treatment's efficacy. However, when it is not logistically possible to conduct an RCT, other sources of obtaining reliable evidence should not be ruled out. The principles and alternative strategies outlined in this work can help to effectively ascertain the efficacy of an intervention in the case of rare diseases.

References

1. JAMA patient page. Medical research. Finding the best information. *JAMA*. 2000;284:1336.
2. Djulbegovic B, Soares HP, Kumar A. What kind of evidence do patients and practitioners need: evidence profiles based on 5 key evidence-based principles to summarize data on benefits and harms. *Cancer Treat Rev*. 2006;32:572-576. Epub 2006 Aug 17.
3. Hampton T. Rare disease research gets boost. *JAMA*. 2006;295: 2836-2838.
4. Djulbegovic B. Acknowledgment of uncertainty: a fundamental means to ensure scientific and ethical validity in clinical research. *Curr Oncol Rep*. 2001;3:389-395.
5. Hastie R, Dawes RM. *Rational Choice in an Uncertain World: The Psychology of Judgment and Decision Making*. Thousand Oaks, Calif: Sage Publications; 2001.
6. Silverman WA, Chalmers I. Casting and drawing lots: a time-honoured way of dealing with uncertainty and for ensuring fairness. The James Lind Library 2002. Available at: http://www.jameslindlibrary.org. Accessed February 27, 2007.
7. Djulbegovic B, Kumar A, Soares H. What is the probability that new cancer treatments are better than standard treatments? *J Clin Oncol*. 2006; 24:18S.
8. Djulbegovic B. Articulating and responding to uncertainties in clinical research. *J Med Philosophy*. 2007. In press.
9. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134:663-694.
10. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ*. 2001;323:42-46.
11. Ioannidis JP. Why most published research findings are false. *PLoS Med*. 2005;2:e124. Epub 2005 Aug 30.
12. Peters WP, Ross M, Vredenburgh JJ, et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol*. 1993;11: 1132-1143.
13. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408-412.
14. Wheatley K. SAB: a promising new treatment to improve remission rates in AML in the elderly? *Br J Haematol*. 2002;118:432-433.
15. Juni P, Egger M. Commentary: empirical evidence of attrition bias in clinical trials. *Int J Epidemiol*. 2005;34:87-88. Epub 2005 Jan 13.
16. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000; 92:205-216.

17. Simes RJ. Publication bias: the case for an international registry of clinical trials. *J Clin Oncol*. 1986;4:1529-1541.
18. Halpern SD, Karlawish JH, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA*. 2002;288:358-362.
19. Chalmers I, Altman DG, eds. *Systematic Reviews*. London: BMJ Publishing Group; 1995.
20. Jadad AR. *Randomised Controlled Trials: A User's Guide*. London: BMJ Books; 1998.
21. *The Impact of Randomized Clinical Trials on Health Policy and Medical Practice: Background Paper*. Washington, DC: US Congress, Office of Technology Assessment, OTABP-H-22; August 1983.
22. Ioannidis JP, Haidich AB, Pappa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA*. 2001;286:821-830.
23. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res*. 2004;4:38.
24. Guyatt G, Vist G, Falck-Ytter Y, et al. An emerging consensus on grading recommendations? *ACP J Club*. 2006;144:A8-9.
25. Cheng AL, Chen YC, Wang CH, et al. Direct comparisons of peripheral T-cell lymphoma with diffuse B-cell lymphoma of comparable histological grades: should peripheral T-cell lymphoma be considered separately? *J Clin Oncol*. 1989;7:725-731.
26. Kwak LW, Wilson M, Weiss LM, et al. Similar outcome of treatment of B-cell and T-cell diffuse large-cell lymphomas: the Stanford experience. *J Clin Oncol*. 1991;9:1426-1431.
27. Savage KJ. Aggressive peripheral T-cell lymphomas (specified and unspecified types). *Hematology Am Soc Hematol Educ Program*. 2005: 267-277.
28. Armitage JO, Vose JM, Weisenburger DD. Towards understanding the peripheral T-cell lymphomas. *Ann Oncol*. 2004;15:1447-1449.
29. Djulbegovic B. Principles of research synthesis. In: Perry M, ed. ASCO Educational Session, 39 Annual Meeting. Washington, DC: ASCO; 2003;737-750.
30. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ*. 1995;311:1621-1625.
31. Gallin JI, Alling DW, Malech HL, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. *N Engl J Med*. 2003;348:2416-2422.
32. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood*. 1997;89:3909-3918.
33. Lara PN Jr, Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. *J Clin Oncol*. 2001;19:1728-1733.
34. Djulbegovic B. Non-randomized trials that changed medical practice. Available at: http://www.hsc.usf.edu/~bdjulbeg/oncology/NON-RCT-practice-change.htm. Accessed February 27, 2007.
35. Brandstatter E, Gigerenzer G, Hertwig R. The priority heuristic: making choices without trade-offs. *Psychol Rev*. 2006;113:409-432.
36. Glasziou P, Chalmers I, Rawlins M, et al. When are randomised trials unnecessary? Picking signal from noise. *BMJ*. 2007;334:349-351.
37. Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd ed. London: BMJ Publishing Group; 2001.
38. Clark O, Clark L, Djulbegovic B. Is clinical research still too haphazard? *Lancet*. 2001;358:1648.
39. Rosenberg W, Donald A. Evidence based medicine: an approach to clinical problem solving. *BMJ*. 1995;310:1122-1126.
40. Clarke M. Doing new research? Don't forget the old. *PLoS Med*. 2004;1:e35. Epub 2004 Nov 30.
41. Lilford RJ, Djulbegovic B. Uncertainty about clinical equipoise: equipoise and uncertainty principle are not mutually exclusive. *BMJ*. 2001; 322:795.
42. Courtney H, Kirkland J, Viguerie P. Strategy under uncertainty. *Harv Bus Rev*. 1997;75:66-79.
43. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987;317:141-145.
44. Weijer C, Shapiro SH, Cranley Glass K. Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomized trial: for and against. *BMJ*. 2000;321:756-758.
45. Spiegelhalter DJ, Myles JP, Jones DR, et al. Methods in health service research: an introduction to bayesian methods in health technology assessment. *BMJ*. 1999;319:508-512.
46. Tan SB, Dear KB, Bruzzi P, et al. Strategy for randomised clinical trials in rare cancers. *BMJ*. 2003;327:47-49.