



December 1, 2008

Kevin J. Cullen, MD  
Director, University of Maryland  
Marlene and Stewart Greenebaum Cancer Center  
22 South Greene Street  
Baltimore, MD 21201

Dear Dr. Cullen:

This letter is written in follow-up to our recent discussions about Medicare coverage of routine patient care costs for beneficiaries participating in phase I cancer clinical trials. As the world's leading professional and scientific organizations representing oncology cancer care professionals, we write to affirm our position that phase 1 cancer clinical trials are the essential gateway for advancement of new cancer treatments—and a vital component of our cancer treatment armamentarium.

It is the view of the undersigned organizations that the current Medicare National Coverage Determination (NCD) (310.1) for Routine Costs in Clinical Trials explicitly includes coverage of phase I cancer clinical trials and that these trials should be covered.

#### **Requirements for Medicare Coverage**

The NCD lays out three basic requirements for Medicare coverage:

- The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).
- The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.
- Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

The NCD also requires that clinical trials covered under the policy have seven “desirable characteristics.”

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;

3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;
6. The trial is in compliance with Federal regulations relating to the protection of human subjects; and
7. All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

The policy also states that certain trials “are presumed to meet these characteristics and are automatically qualified to receive Medicare coverage.” Trials that are automatically deemed include:

1. Trials funded by NIH, CDC, AHRQ, CMS, DOD, and VA;
2. Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, CMS, DOD and VA;
3. Trials conducted under an investigational new drug application (IND) reviewed by the FDA; and
4. Drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place. At that time the principal investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial and will not be used to retroactively change the earlier deemed status.”

### **Phase 1 Cancer Clinical Trials Have Therapeutic Intent**

The National Cancer Institute’s (NCI) Investigator Handbook is instructive as to the therapeutic intent of a Phase I trial. That handbook includes the following information about phase 1 cancer clinical trials (emphasis added):

Phase 1 trials determine a safe dose for Phase 2 trials and define acute effects on normal tissues. In addition, these trials examine the agent's pharmacology and may reveal evidence of antitumor activity. **Therapeutic intent is always present in Phase 1 trials**; indeed, anticancer agents are not tested in patients unless preclinical activity studies have already demonstrated evidence of significant activity in laboratory models.<sup>1</sup>

The Food and Drug Administration (FDA) has also adopted a definition of phase 1 trials that is consistent with the NCI’s definition. FDA states that phase 1 studies “are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to **gain early evidence of effectiveness**.” This early evidence of effectiveness is the grounding for therapeutic intent – both in the choice of oncologists and patients to enroll in the trial, and as one of the aims of the trial.

Although the scientific goals of a phase 1 trial are to determine the toxic effects, pharmacologic behavior, and recommended doses for future study of a new agent, there is always a strong preclinical

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<sup>1</sup> Available on the NCI website at <http://ctep.cancer.gov/handbook/index.html>

rationale for bringing the drug into the clinic with the expectation of positive clinical outcomes for some patients.<sup>2</sup> In fact, Institutional Review Boards would not permit the administration of potentially toxic treatments to patients unless there was some reasonable prospect of antitumor effect.<sup>3</sup> It is also important to note that phase 1 oncology treatment trials are **never** done in healthy volunteers because of the potential toxicities associated with the treatments under investigation.

Additionally, many of the NCI phase 1 trials involve agents that are already approved for the treatment of one type of cancer and are being studied in a different type of cancer, or in combination with other treatments. As a result, we have some evidence of therapeutic effectiveness that provides solid grounding on which to base therapeutic intent. Indeed, an analysis of 12,000 individuals who participated in 460 NCI-funded phase 1 trials done in 2005 found that 10.6% of patients experienced an objective response. This number increased to 17.8% of patients when one drug included in the trial regimen was already FDA-approved.<sup>4</sup>

Furthermore, our growing knowledge of the molecular basis of cancer is allowing us to increasingly develop treatments that are targeted to particular molecular pathways and personalized to specific patient populations. These types of agents will provide a “high pretreatment probability of achieving both an objective response and more subjective clinical benefit” for the trial participants.<sup>5</sup>

To bring about these exciting new developments in cancer treatment, clinical trials participation is required. It is particularly important in the Medicare-aged population not only because of the increased incidence of cancer in the elderly and but also to develop our understanding of how treatments work in this population. Both the NCI and FDA definitions demonstrate that phase 1 oncology trials meet the requirements for Medicare coverage, including therapeutic intent, and should be covered.

Sincerely,



Raymond N. DuBois, MD, PhD  
President  
American Association for  
Cancer Research



Edward J. Benz, Jr., MD  
President  
Association of American  
Cancer Institutes



Richard L. Schilsky, MD  
President  
American Society of  
Clinical Oncology

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<sup>2</sup> ASCO: Critical role of phase 1 clinical trials in cancer treatment. J Clin Oncol 15:853-859, 1997.

<sup>3</sup> Kodish E, Stocking C, Ratain MJ, et al: Ethical issues in phase I oncology research: A comparison of investigators and IRB chairpersons. J Clin Oncol 10:1810-1816, 1992.

<sup>4</sup> Horstmann E, McCabe MS, Grochow L, et al: Risks and benefits of phase 1 oncology trials, 1991 through 2002. New Engl J Med 352:895-905, 2005.

<sup>5</sup> Markman M: Further evidence of clinical benefits associated with participation in phase 1 oncology trials. B J Cancer 98:1021-1022, 2008.