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COMMENTS AND CONTROVERSIES

Responsibility for Costs Associated With Clinical Trials

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Medicare and coverage requirements in the Patient Protection and Affordable Care Act (ACA) have improved access to clinical trials, but major obstacles persist. First, access to participation in studies can be limited if networks established by insurance plans do not include providers involved in clinical trials. Second, certain details of the relationship between the clinical trials provisions of the ACA and state laws have not been defined. Third, consensus regarding the scope of insurance coverage for costs in clinical trials has not been reached. We discuss each of these problems and offer suggestions for resolution. These obstacles must be addressed to improve access for patients and to advance medical care through research.

Advances in treatments and medications continue at a rapid pace and demonstrate the ability to improve health care outcomes through clinical trials. Patients struggling with chronic, debilitating, and life-threatening diseases must have access to all reasonable avenues of possible benefit, including any appropriate clinical trials that are open for enrollment. Many insurance plans, however, provide no coverage for clinical trials because of concerns about liability for the added costs of research-related complications and services, items, or tests.

Limited studies have shown that direct patient care costs in clinical trials are not substantially higher than in the absence of a clinical trial.[1,2] Historically, sponsors, employers, third party payers, health care institutions and study participants have shared the overall costs of clinical trials. Each of these stakeholders has the potential for short and long-term gain by maintaining a shared, but fair, distribution of these costs.

On June 7, 2000, President Clinton signed an executive order requiring that Medicare reimburse for all routine patient care costs for patients participating in clinical trials.[3] The executive order cited a report published by the Institute of Medicine[4] advocating for an increase in the use of clinical trials by older Americans. As a result, Medicare has since reimbursed routine costs that fall within a Medicare benefit category for patients who participate in clinical trials with therapeutic intent for patients with diagnosed disease and for items and services that are reasonable and necessary in diagnosing and treating complications arising from participation in all clinical trials. Medicare does not cover investigational items and services or services provided solely for the purpose of data collection and analysis.[5]

Section 2709 of the ACA sets forth a national minimum coverage standard and outlines new requirements for coverage of patients participating in approved clinical trials.[6] Unlike Medicare, ACA provisions for coverage include clinical trials of any phase that are conducted in relation to the "prevention, detection, or treatment of cancer or other life-threatening disease or condition . . .."[7] The clinical trial must have been approved or funded by a federal organization, be conducted under an investigational new drug application reviewed by the US Food and Drug Administration, or be a drug trial that is exempt from the US Food and Drug Administration application review process, similar to characteristics that qualify for Medicare coverage.

To receive clinical trial coverage under the ACA, a patient must be covered by a health plan and be "eligible to participate in an approved clinical trial according to the trial protocol with respect to treatment of cancer or other life-threatening disease or condition."[8] The ACA also requires that "the referring health care professional is a participating health care provider [who] has concluded that the individual's participation in such trial would be appropriate" or the "beneficiary provides medical and scientific information establishing that the individual's participation in such trial would be appropriate."[9]

If these requirements are met, routine patient costs, including all items and services that are typically covered for a qualified patient who is not enrolled onto a clinical trial, are covered similar to Medicare rules. The ACA excludes from coverage any investigational items, including those provided only for purposes of data collection and analysis rather than direct clinical management of the patient. The ACA also excludes from coverage any services that are "clearly inconsistent with widely accepted and established standards of care for a particular diagnosis."[10] These provisions are similar to those that apply for Medicare coverage.

The ACA takes the important step of providing a minimum coverage standard for clinical trials, but gaps remain. No rulemaking has been promulgated to provide additional guidance and clarity, and enforcement is lacking to ensure that health insurance providers provide coverage for qualified clinical trials. Instead, the Department of

Health and Human Services expects that plans and issuers will adhere to ACA provisions in good faith.[11]

In the ACA legislation, out-of-network coverage for clinical trials is required only in plans that otherwise provide coverage for out-of-network services.[12] Patient access to clinical trials could be effectively denied when plans that have too few clinical trial providers in the network do not cover out-of-network services. To improve access, out-of-network services should be covered when the network does not include providers who offer an appropriate clinical trial or when the only in-network sites that offer such trials are located far from a patient's home.

The relationship between clinical trial provisions of the ACA and state laws remains to be clarified. Thirteen states do not mandate coverage for phase I studies or do so only on a case-by-case basis. In many states, existing laws do not require coverage of procedures deemed experimental or research-related.[13,14] At present, 36 states require issuers to provide some level of coverage for clinical trials, although the coverage may be minimal in some instances.[13] The Employee Retirement Income Security Act preempts state law and precludes states from applying benefit mandates to plans offered by self-insured groups, thereby limiting access to clinical trials for patients enrolled in these plans. It remains unclear whether provisions of the ACA mandating coverage for clinical trials apply to plans offered by self-insured groups. Regulations are needed to clarify the extent to which the ACA provisions require coverage and reimbursement for clinical trials, and they should be written in ways that do not impede access to clinical trials.

Consensus has not yet been reached regarding the scope of coverage for the costs of services, items and tests related to clinical trials. Medicare and the ACA offer a template for defining the scope of clinical trial coverage that should be extended to all insurance plans. The following guiding principles serve as important components of this template (Table 1). First, insurance plans should include coverage for clinical trials that have therapeutic intent and offer a reasonable possibility of benefit to the patient. Although determining efficacy is not the primary intent of phase I protocols, these studies have therapeutic intent when secondary end points include an assessment of the disease response produced by an investigational intervention. Sponsors have a corresponding obligation to explain the rationale for believing that the trial offers genuine potential for benefit for patients who participate. Sponsors also have an obligation to design the eligibility criteria for clinical trials with therapeutic intent in a way that includes patients who could benefit while excluding those who are likely to be harmed. We recognize that the term *reasonable* remains difficult to define, and judgments are likely to differ from one situation to the next.

Table 1. Proposed Principles of Policy on Responsibility for Costs Associated with Clinical Trials

Principle
To ensure language consistency, the terms *standard of care costs*, *usual care costs*, and *routine care costs* should be abandoned and replaced with any test, procedure, medicine, or other intervention that is for "the direct clinical management of the patient" or that is "reasonable and medically necessary" to ensure safety.
Insurance plans should include coverage for clinical trials that have therapeutic intent and offer a reasonable possibility of benefit to the patient.
Insurance plans should cover trial-associated costs for items and services required in "the direct clinical management of the patient" and for those that are "reasonable and medically necessary" to ensure safety.
Sponsors should cover trial-associated costs for the investigational items, tests or services themselves and for services that are provided solely for the purpose of data collection and analysis.
As an integral part of the trial design, a coverage analysis should identify payment for each item, test and service required by a clinical protocol as a sponsor responsibility or as a patient or insurance provider responsibility.

Second, ill-defined terms such as *standard of care costs*, *usual care costs*, and *routine care costs* should be abandoned as a basis for determining coverage. A universally accepted definition of the standard of care remains elusive, and the concept "has evolved over the years and will continue to change."[15] In absence of a clear and universally applicable definition, insurance providers have wide latitude in determining coverage for clinical trials when the standard of care is used as the criterion. The variability of language in insurance documents and the uncertainties of clinical trial coverage can present substantial barriers to patients seeking their preferred course of treatment.

Instead, insurance plans should follow the lead provided by Medicare and the ACA in covering trial-associated costs for items and services required in "the direct clinical management of the patient" and for those that are "reasonable and medically necessary" to ensure safety. Accordingly, insurance plans should cover the costs of chemotherapy medications given together with an investigational medication as part of a combination regimen. Early-phase clinical trials require testing to demonstrate safety, even if preclinical results do not support a specific concern. For example, frequent ECGs are often required to determine whether a new drug causes abnormal electrical conduction in the heart. These tests could be considered medically necessary to ensure patient safety, particularly if the drug class is known to be associated with cardiac conduction abnormalities. The same tests might be required solely for data purposes if the drug class has not been associated with cardiac conduction abnormalities or if the frequency of testing far exceeds the level needed to ensure patient safety. Direct discussion between sponsors and insurance payers could help define the boundaries of medical necessity more clearly.

Third, sponsors should cover trial-associated costs for the investigational items or services themselves and for services that are provided solely for the purpose of data collection and analysis. This principle also follows the lead provided by Medicare and the ACA. An unresolved question is who should cover the costs of routine surveillance radiographic or nuclear medicine imaging of asymptomatic patients at late time points in cancer treatment trials using survival without progression of malignancy as an end point. In some situations, early detection of recurrent malignancy in an asymptomatic patient might offer information that is truly helpful in the direct clinical management of the patient, but in other situations, such early detection offers no demonstrable long-term advantage over later detection through the onset of symptoms, signs, or simple laboratory abnormalities.[16,17]

Fourth, as an integral part of the trial design, the sponsor should provide a coverage analysis identifying payment for each item, test, and service required by a clinical protocol as a sponsor responsibility or as a patient or insurance provider responsibility. This determination is currently made through negotiations between sponsors and the institutional representatives of an investigator who would like to enroll patients onto a trial. Once this agreement is reached, investigators

and their institutional representatives must then negotiate with insurance payers to determine which items will actually be covered for each patient who is enrolled onto the trial. This extremely inefficient process should be replaced by making the allocation of costs and the coverage analysis as transparent as possible in the protocol document, thereby enabling truly informed decisions by investigators, patients, and insurance payers. When appropriate, the protocol document should explain how items and services required by a clinical trial are related to "the direct clinical management of the patient" or why items and services are "reasonable and medically necessary" to ensure safety. Clarifying sponsor versus patient or insurance responsibilities and those components in the trial that are essential to monitor safety and efficacy should enhance reviews by institutional review boards, patients, employers, and other payers.

We believe that reimbursement for "the direct clinical management of the patient" must be applicable to all types of clinical trials to ensure that researchers conduct them in a safe manner and at the same time account for each patient's unique circumstances. The understanding of "reasonable and medically necessary" and "for the direct clinical management of the patient" should encompass biopsies, laboratory tests, scans, imaging, and other procedures that are needed to select appropriate patients to participate in the study and to assess safety and efficacy. Many procedures performed as part of a clinical trial are classified by insurance providers as investigational or experimental, excluding them from coverage, even though they may be medically necessary within the context of the specific clinical trial. Therefore, we emphasize the importance of defining and justifying medical necessity within the context of a clinical trial, thus allowing for coverage of necessary services and providing clarity for all parties, including patients, institutional review boards, employers, and other payers. Collaborative efforts between sponsors, investigators and insurance would help to ensure that patients have all appropriate opportunities to participate in clinical trials, consistent with the intent of Medicare and the ACA.

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