June 25, 2018

Ms. Seema Verma
Administrator
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Attention: CMS-1694-P
P.O. Box 8011
Baltimore, MD 21244-1850

RE: CMS-1694-P; Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Proposed Policy Changes and Fiscal Year 2019 Rates

Dear Ms. Verma:

I am writing on behalf of the American Society of Hematology (ASH) to provide the following comments on the CY 2019 Hospital Inpatient Prospective Payment System proposed rule. We appreciate the opportunity to provide these comments to the Centers for Medicare and Medicaid Services (CMS) on the provisions impacting our members.

ASH represents over 17,000 clinicians and scientists worldwide, who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sick cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients in diverse settings including teaching and community hospitals, as well as private practice.

ASH looks forward to working closely with the agency as these proposals are implemented and offers the following comments on issues of particular importance to our members:

1. Chimeric Antigen Receptor (CAR) T-Cell Therapy Reimbursement
2. Payment Rate for Hematopoietic Cell Transplantation
3. New Technology Payment for AML Therapy

Chimeric Antigen Receptor (CAR) T-Cell Therapy Reimbursement

ASH would first like to thank CMS for responding to inquiries requesting that the agency address payment of CAR T-cell therapy under the Inpatient Prospective Payment System (IPPS). Our members are delivering the two FDA-approved products, KYMRIAH™ and YESCARTA™, as well as administering new CAR-T therapies in ongoing clinical trials. They are witnessing the promise it holds for a medically vulnerable patient population. The Society’s goal is to protect access for appropriate patients to receive CAR-T therapy and to ensure equitable reimbursement for the PPS-reimbursed and PPS-exempt cancer centers delivering this therapy.
CAR-T therapy is transformative and represents a new method to treat cancer patients. Patients receiving CAR-T therapy are the sickest of the sick and have typically exhausted all other treatments, including chemotherapy, radiation, or stem cell transplant. It can bring a potentially life-saving option to patients whose care needs are currently unmet by existing therapeutics and who would otherwise receive high-cost, ineffective treatments.1

With over 400 clinical trials in process, it is impossible to know what the ultimate applications of this therapy will be. The current approved applications to hematologic malignancies are just the first conditions to which CAR T-cell therapy will apply. The next CAR T-cell therapy targeting multiple myeloma is expected to be approved in 2019. There are numerous clinical trials underway for both blood cancers, including multiple myeloma and acute myeloid leukemia, and solid tumors, including ovarian, breast, pediatric neuroblastoma, and lung cancer.2 Besides the likelihood that CAR T-cell therapy will be more broadly available within the next decade, ASH also wants the agency to understand as it formulates its payment policy, that the science and its clinical application will change as well. It is imperative that the agency formulate policy that can evolve with the science.

ASH urges CMS to develop an innovative payment solution to protect patient access. We recognize that the agency articulated a unique proposal that includes a cost-to-charge ratio (CCR) of 1.0 and a revised MS-DRG 016, Autologous Bone Marrow Transplant with CC/MCC or T-cell Immunotherapy, to reimburse for this costly therapy. However, we do not believe CMS’ proposal as outlined will provide equitable reimbursement for this innovative treatment, limiting patient access when institutions determine they cannot afford to deliver this therapy. Institutions currently providing CAR-T therapy outside of clinical trials are grappling with how to absorb significant losses on the cost of the product and the care.

Because CMS will be setting a significant precedent with its final payment policy for CAR-T therapy, we urge the agency to work with ASH and other interested stakeholders to ensure this policy meets the needs of patients, providers, and the agency. CMS invited public comments on both the agency’s proposed approach and any alternatives. In the Alternative Reimbursement Proposal section of these comments (below), ASH offers an alternative that we believe will both provide equitable reimbursement and protect patient access. An added benefit of this alternative is that it creates a product agnostic, site neutral payment structure. The high cost of both FDA-approved products reinforces the need to remove site of service incentives. The agency noted in the proposed rule that stakeholders preferred establishing a payment that is comparable in both the inpatient and outpatient settings. Patients should be treated in the appropriate medical setting where they will receive the best care for their condition, not the site of service that provides the highest margin.

**Background on CAR T-cell Therapy**

CAR-T therapy is currently approved for the treatment of patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. It is also approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Patients eligible for CAR T-cell therapy have typically exhausted all other treatment options, including chemotherapy, radiation, or stem cell transplant. Twenty to 50% of patients with DLBCL, the most common subtype of non-Hodgkin lymphoma, will be refractory to the standard treatment regimen or will relapse after achieving complete response. Even among patients with relapsed or refractory DLBCL who respond to salvage

---


therapy and are able to undergo autologous stem cell transplantation (ASCT), about 50% will ultimately relapse after transplantation. The prognosis for these patients is poor, especially for those who have high-risk factors. Thus, most patients with refractory DLBCL have no curative treatment options. CAR T-cell therapy truly is lifesaving for eligible patients.

Currently, each treatment is individual to the patient whose T-cells are genetically engineered to target a specific tumor-associated antigen. Cells are collected from patients via leukapheresis and then delivered to the manufacturer where the molecularly engineered receptors are inserted into the cells and then reproduced, a process that takes weeks. The new CAR T-cells are then returned to the hospital where they are infused into the patient. Most patients suffer from serious adverse events in the days following the infusion that may require prolonged hospital stays. The therapy can have tremendous benefits, as we have described, but requires very close oversight by the treating physician during and following the treatment.

**Adverse Events**

The two most common adverse events are cytokine-release syndrome (CRS) and CAR T-cell-related encephalopathy syndrome (CRES). CRS, triggered by the T-cells engaging with the tumor cells, is the most common adverse event experienced by about 70 percent to 90 percent of patients. It manifests as a very severe case of the flu with high fever, fatigue and body aches, and can affect any organ system in the body. The onset of CRS usually occurs within the first week after CAR T-cell therapy, and typically peaks within one to two weeks of cell administration. In order to closely monitor for CRS, it is recommended that patients remain hospitalized for at least seven days after CAR T-cell infusion. With CRES, patients can become confused and disoriented, experience language disturbance and impaired handwriting, and sometimes may not be able to speak at all for a few days. This condition can also be managed, and patients regain all of their neurological functions.

These adverse events require care in the intensive care unit (ICU) setting and high-cost supportive care medications. In the report from the “JULIET” trial that assessed the effectiveness of tisagenlecleucel in the treatment of patients with relapsed or refractory NHL, of 99 patients who received the treatment, 86% had grade 3-4 adverse events with CRS occurring in 58% of the patients and another 12% experiencing neurological toxicity. In other clinical trials involving either tisagenlecleucel and axicabtagene ciloleucel, these life-threatening toxicities were reported in a substantial number of patients. Neelapu, et al reported grade 3 or higher CRS and neurotoxicity in 13% and 38%, respectively, of patients who received axicabtagene ciloleucel for treatment of B-cell lymphomas. In a multicenter phase 2 trial of tisagenlecleucel in pediatric/young adult patients with CD19+ ALL, CRS and neurological toxicities were reported in 77% and 40% of patients, respectively.

It is important to note that adverse events are usually manageable but do increase the cost of this therapy as patients are typically required to be admitted as inpatients for treatment. These inpatient stays must be factored into an appropriate reimbursement mechanism.

**Alternative Reimbursement Proposal**

---


6 Neelapu SS, “Chimeric antigen” (footnote 3).

ASH worked closely with the American Society of Blood and Marrow Transplantation (ASBMT) as well as other provider groups to review the agency’s proposal and to consider alternative payment options. Our goal in reviewing all options was fourfold: 1) to identify a payment option that would avoid creating financial barriers for Medicare beneficiaries; 2) to create a site-neutral, product-agnostic payment structure; 3) to create a system that accommodates pricing of future innovative products; and 4) to identify a solution that will address the needs of the PPS-reimbursed and PPS-exempt centers. As we have described above, CAR-T therapy differs from traditional cancer therapies in terms of the product preparation and administration, as well as the complexity of the adverse events that typically occur. An equitable Medicare payment must account for both the cost of the product and the cost of care.

The option that CMS proposed (the revised MS-DRG 016 and a CCR of 1.0) along with a New-Technology Add-on Payment (NTAP) for the products would result in a loss of approximately $65,000 (see Attachment 1) for PPS-reimbursed institutions. The Society appreciates that this solution would help address the mark-up issues stemming from the high cost of the product; however, ASH believes this estimated loss is conservative because the revised MS-DRG 016 does not account for the cost of the ICU stays required to treat the adverse events experienced by the typical CAR-T patient. The typical autologous transplant patient does not experience adverse events that require admission to the ICU. Implementing CMS’ proposal will create patient access issues because the financial losses for institutions will be unsustainable.

Instead, ASH is proposing the same payment option advanced by ASBMT: implementation of the revised MS-DRG 016 proposed by the agency with a separate CAR-T product payment. This would allow CMS to pay for the cost of care under MS-DRG 016 with its current outlier policy in place and pay for the product cost separately as a pass-through at actual acquisition or invoice cost. It would have the added benefit of being site neutral, eliminating financial incentives to treat patients in settings that may not be medically appropriate. This proposal would also apply a consistent payment rate across CAR-T centers. There would be no winners and losers created from applying IPPS adjustments, including the wage index and DSH, to the cost of the product. CMS would also be able to adjust payment for the product on a quarterly basis when ASP changes rather than having to wait years to adjust a MS-DRG payment. PPS-exempt centers would also limit their losses on the products’ cost if a separate payment were to be applied. We recognize that reimbursing for the product as a pass-through will require the agency to use its adjustment authority. Given the innovative nature of therapy, we believe using this authority is warranted.

ASH notes that this alternate option would still create an estimated shortfall of almost $28,000 (see Attachment 1) for the cost of the care. Again, this estimate is likely conservative because of the differences in care delivered to CAR-T versus autologous transplant patients. The Society considered recommending that CMS create a new MS-DRG for CAR-T therapy rather than use the revised MS-DRG 016 to address this shortfall. Unfortunately, ASH did not have sufficient, reliable data to model a new MS-DRG for the agency. ASH strongly recommends that CMS use revised MS-DRG 016 only until sufficient data is gathered to establish a more appropriate MS-DRG in future rate-setting. We are confident claims will show that MS-DRG 016 does not accurately reflect the costs of the complex care required by these patients. Despite the limitations, ASH is supportive of the alternate option of reimbursing for the revised MS-DRG and the CAR-T product separately because it will create a sustainable payment model that will protect patient access to CAR-T therapy and can be applied to other similar innovative therapies.

The Society recognizes that PPS-exempt cancer centers do not use the MS-DRG system, but we urge CMS to develop a solution that will address the cost of care, as well as the cost of the product for these institutions. ASH recommends the development of an adequate outlier payment protection system for these centers. Their

---

8 Social Security Act §1886(d)(5)(l)(i): “The Secretary shall provide by regulation for such other exceptions and adjustments to such payment amounts under this subsection as the Secretary deems appropriate.”
patients will require the same costly, supportive care as those in PPS-reimbursed institutions. CMS must develop a reimbursement solution to avoid unsustainable losses on the patient care for the PPS-exempt centers. ASH urges CMS to adopt this approach and limit its application to certain therapies to avoid setting too broad a precedent. ASH welcomes the opportunity to work with CMS to determine the appropriate application given our members’ experience and expertise with ongoing clinical trials in this area.

The alternative payment option ASH is recommending does not require the application of a NTAP payment. In the event that CMS does not implement the Society’s alternate payment option outlined in this letter, the Society strongly recommends that CMS grant the application for a NTAP payment. This payment would help institutions address financial losses associated with CAR-T therapy in the short-term and allow CMS and stakeholders to develop a sustainable long-term solution.

ASH’s Recommendation to Establish a Pass-Through Payment for CAR-T Cells is a Logical Outgrowth of the Proposed Rule

The Society’s proposed pass-through payment for the CAR-T product can be adopted in the final rule because it is a logical outgrowth of the proposed rule. More specifically, the preamble of the proposed rule states the following:

We are inviting public comments on our proposed approach of assigning ICD–10–PCS procedure codes XW033C3 and XW043C3 to Pre-MDC MS–DRG 016 for FY 2019. We also are inviting public comments on alternative approaches, including in the context of the pending KYMRIAH™ and YESCARTA™ new technology add-on payment applications, and the most appropriate way to establish payment for FY 2019 under any alternative approaches. Such payment alternatives may include using a CCR of 1.0 for charges associated with ICD–10–PCS procedure codes XW033C3 and XW043C3, given that many public inquirers believed that hospitals would be unlikely to set charges different from YESCARTA™ CAR T-cell therapy drugs, as discussed further in section II.A.4.g.2.of the Addendum of this proposed rule. These payment alternatives, including payment under any potential new MS–DRG, also could take into account an appropriate portion of the average sales price (ASP) for these drugs, including in the context of the pending new technology add-on payment applications. (emphasis added)

In other words, CMS solicited comments on “any alternative approaches” to making payment for CAR-T therapy and that CMS proposed using a CCR of 1.0 for CAR-T cases because it was concerned that hospitals might not mark up the cost of the product sufficiently for charges to reflect the true cost of CAR T-cells.10 Our proposal to establish a pass-through payment for the product is well within the scope of CMS’s solicitation for comments on “any alternative approaches” and with respect to its proposals to (1) establish a new MS–DRG that includes a portion of the ASP of CAR T-cells and (2) establish a CCR of 1.0 for a CAR-T NTAP and outlier payments for cases involving administration of CAR-T cells. The intent of both proposals is to assure that IPPS payments for CAR-T cases take into account the actual cost of CAR-T cells to IPPS hospitals. The

10 See, American Trucking Assoc., Inc. v Fed. Motor Carrier Safety Admin., 724 F.3d 243, 252 (DC Cir Aug. 2, 2013) (finding that a final rule imposing an off-duty break of at least 30 minutes to short haul drivers was a logical outgrowth of the proposed rule, which would have require short-haul drivers to comply with a broader range of regulations which included off-duty breaks);CSX Transp., Inc. v. Surface Transp. Bd., 584 F.3d 1076, 1080 (explaining that “a final rule represents a logical outgrowth where the NPRM expressly asked for comments on a particular issue or otherwise made clear that the agency was contemplating a particular change” and contrasting that with cases where the “proposed rule gave no indication that the agency was considering a different approach”); United Steelworkers of America, etc. v Marshall, 647 F2d 1189 (D.C. Cir. 1980), cert. den. 453 US 913 (1981) (upholding a final workplace safety rule limiting employee exposure to airborne lead in concentrations greater than 50 micrograms per cubic meter and have different phase in periods for different industries, although OSHA had proposed to lower the permissible exposure level to 100 micrograms per cubic meter for all industries). See also, Spartan Radiocasting Co. v Federal Communications Comm’n., 619 F2d 314 (4th Cir. 1980) (holding that a NPRM must be sufficient to fairly apprise interested parties of the issue involved but need not specify every precise proposal that the agency may ultimately adopt as a rule).
intent of our proposal for a pass-through payment for CAR T-cells is exactly the same as the intent of the CMS proposals and the results would be similar. In summary, interested parties were apprised generally of the intent to include the true cost of CAR T-cells in IPPS payments. Comments proposing a different means to achieve exactly the same goal would, therefore, clearly be a logical outgrowth of the proposed rule.

**Payment Rate for Hematopoietic Cell Transplantation**

ASH remains concerned that the inadequate Medicare reimbursement rate for bone marrow, cord blood, and peripheral blood stem cell transplants, collectively known as hematopoietic cell transplantation (HCT), has created a barrier to care for Medicare beneficiaries in need of such a transplant. The Society is disappointed that this issue is not addressed in the proposed rule.

HCT is the standard of care for more than 70 diseases, including blood cancers, such as leukemia and lymphoma. Cell acquisition costs vary and are dependent on clinical factors as well as cell source. In 2018, adult donor cells from marrow and peripheral blood stem cells (PBSC) had an average cost of $49,426 while the average cost of cord blood was $64,864. The average inpatient hospital stays for this transplant averages 27.45 days. With these acquisition costs and average of length of stay, the Medicare reimbursement does not cover the hospitals’ costs of providing the service. It is not sustainable for hospitals to continue performing this service at this reimbursement rate and may negatively impact patient access.

ASH requests that CMS take action to avoid this patient access issue by using existing authority to reimburse the cell acquisition costs for HCT in the same way it reimburses for solid organ donors. Solid organ transplant programs receive a payment separate from the MS-DRG for the cost of locating and purchasing the organ used for transplant. If the acquisition cost for donor cells and cord blood was reimbursed on reasonable cost basis, hospitals would be able to cover their costs under the MS-DRG for HCTs, eliminating the threat to patient access.

While ASH is supportive of H.R. 4215, the Protect Access to Transplant (PACT) Act, which would ensure that hospitals providing HCT to Medicare beneficiaries receive adequate payments, similar to what hospitals receive for solid organ transplants, the Society believes that CMS has the authority to make this change. Short of that, we request that CMS work directly with Congress, urging them to pass H.R. 4215.

**VYXEOS New Technology Add-on Payment**

In the proposed rule, CMS invites public comment on the VYXEOS New Technology Add-on Payment (NTAP) application. VYXEOS, a liposomal formulation containing a fixed combination of cytarabine and daunorubicin in a 5:1 molar ratio, was developed to treat patients with high-risk (secondary) acute myeloid leukemia (AML). The current standard of care regimen of cytarabine and daunorubicin is known as 7+3. After consulting with ASH members who treat patients with high-risk acute AML and have used VYXEOS therapy, ASH recommends CMS approve the VYXEOS NTAP application.

Specifically, CMS asked if VYXEOS is substantially similar to existing technology, including whether the mechanism of action of VYXEOS differs from the mechanism of action of the current treatment regimen, specifically the 5:1 molar ratio of VYXEOS compared to the free-drug dosing of cytarabine and daunorubicin. According to ASH members who use this product, VYXEOS is not substantially similar to existing technology; it is a unique drug combination. Furthermore, the mechanism of action of VYXEOS differs from the mechanism of action of the current treatment regimen. The increased ratio of drug is facilitated by the liposomal formulation, which is a substantial improvement for patients.

CMS also asked if the clinical results of the VYXEOS Phase III Study 301 represent substantial clinical improvement, specifically with respect to overall survival rate, lower risk of early death, improved response
rates, better outcomes following transplant, increased response rate and overall survival in patients diagnosed with FLT3 mutation, and higher response rates versus conventional “salvage” chemotherapy in younger patients diagnosed with poor-risk first relapse. According to data, the clinical results of the VYXEOS Phase III Study 301 represent substantial clinical improvement, specifically overall survival rate, lower risk of early death, and improved response rates, as follows:

- The median overall survival for patients treated with VYXEOS in the study was 9.56 months compared to 5.95 months for patients receiving 7+3.
- The percentage of patients alive 12 months after randomization was 41.5% on the VYXEOS arm compared to 27.6% on the 7+3 arm.
- The percentage of patients alive 24 months after randomization was 31.1% on the VYXEOS arm compared to 12.3% on the 7+3 arm.
- There is data showing that patients who go to transplant have a two-year survival in the 65% range.

Finally, CMS asked if the overall improvement in survival from 5.95 months (VYXEOS) to 9.56 months (7+3 free-drug dosing) represent a substantial clinical improvement. ASH members agree that four months of difference represents a substantial clinical improvement for patients.

Based on the feedback from ASH members who treat patients with high-risk acute AML and have used VYXEOS therapy, the Society recommends CMS approve the VYXEOS NTAP application.

Summary
Thank you for the opportunity to provide comments on reimbursement for CAR-T therapy, a new payment rate for hematopoietic cell transplantation, and a new technology payment for AML therapy. The Society would like to stress that CAR-T technology is the beginning of a growing, robust future pipeline of innovative, life-saving therapeutics that are profoundly distinct from current anti-cancer treatments. The need for an equitable reimbursement model is essential to allow institutions to deliver these treatments in a financially sustainable manner. We welcome the opportunity to discuss these proposals, and others being considered with you and your team. If you have any questions or require further clarification, please contact Leslie Brady, ASH Policy and Practice Manager at lbrady@hematology.org or 202-292-0264.

Sincerely,

Alexis Thompson, MD, MPH
President
<table>
<thead>
<tr>
<th>Option Description</th>
<th>FY 2018 Status Quo</th>
<th>Auto MS-DRG (or equivalent) and NTAP Approved</th>
<th>Auto MS-DRG, CCR of 1.0 and NTAP</th>
<th>Auto MS-DRG and a Separate CAR-T Product Payment Based on ASP or some equivalent (e.g., actual acquisition cost reported on claim)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS-DRG</td>
<td>840 or other</td>
<td>016</td>
<td>016</td>
<td>016</td>
</tr>
<tr>
<td>Outlier</td>
<td>Current methodology</td>
<td>Current methodology</td>
<td>Product acquisition cost used to implement a CCR of 1.0</td>
<td>Outlier applied with the current CCR excluding the CAR-T product cost</td>
</tr>
<tr>
<td>NTAP</td>
<td>Not available</td>
<td>Approved</td>
<td>Approved</td>
<td>No NTAP per se since the CAR-T acquisition cost paid as a pass-through</td>
</tr>
<tr>
<td>Financial Impact Based on Hospital with 10% Mark up</td>
<td>($319,999)</td>
<td>($304,425)</td>
<td>($62,750)</td>
<td>($17,069)</td>
</tr>
<tr>
<td>Financial Impact Based on Hospital with 400% Mark up</td>
<td>($103,659)</td>
<td>($62,750)</td>
<td>($62,750)</td>
<td>($17,069)</td>
</tr>
</tbody>
</table>

*From analysis done by ASBMT*