University of Wisconsin
MEDICAL SCHOOL

March 10, 2006

Steve Phurrough, MD., Director
Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Boulevard, C1-09-06
Baltimore, MD 21244

Re: Comments on Proposed Decision Memo on Formal Request for Reconsideration of National Coverage Decision for Intestinal and Multivisceral Transplantation (CAG-00036R)

Dear Dr. Phurrough:

The University of Wisconsin in Madison (University) appreciates the opportunity to respond to the Centers for Medicare and Medicaid Services' (CMS) proposed decision memo on our request for Reconsideration of its National Coverage Decision for Intestinal and Multivisceral Transplantation (CAG-00036R). The University previously requested that CMS reconsider its initial decision not to revise its National Coverage Decision (NCD) on Intestinal and Multi-visceral Transplantation (# CAG-00036N). The standard that the University proposes would permit centers that have performed 10 *cumulative* intestinal transplants with one year patient survival of 65 percent (using the Kaplan-Meier technique) to become eligible for Medicare coverage for intestinal and multi-visceral transplantation. This standard is consistent with existing outcomes-based analyses of transplant center statistics and patient safety.

In its proposed decision memo, CMS reviews the evidence from its literature search from 2000 to the present as well as a set of external technology assessments and clinical reviews, and an internal technology assessment and concludes that its current standard is necessary "to ensure that intestinal transplants are furnished in a manner that is reasonable and necessary for the treatment of disease."

The University believes that the data it submitted and the studies it cited as part of its Formal Request for Reconsideration, as well as its response to the comments posted on behalf of Dr. Kareen Abu-Elmaged, support a standard based on 10 cumulative transplants. We also think that the 10 cumulative standard will ensure that intestinal transplants are perfonned in a manner that is reasonable and necessary for the treatment of disease.

Unfortunately, in its proposed decision memo, CMS once more has misinterpreted a set of key studies and erroneously concentrated on the *annual* volume of transplants instead of the *cumulative* number of transplants that are actually used in most of the studies it cites. Therefore, we are taking this opportunity to comment on the studies that CMS uses to justify its decision to remain with an annual volume standard rather than a cumulative volume standard. In doing so, we highlight the standard used in the study or the fact that a standard was not specified. We urge the agency to once more review these studies and accurately reflect their findings in a final decision memo that accepts *cumulative* volume of 10 or more transplants as the basis for Medicare approval.

The question CMS applies to its consideration of the evidence is the correct one:

> What is the evidence on net health benefits for intestinal transplantation provided by facilities that performed 10 procedures annually [the current standard] compared to centers that performed 10 cumulative transplants [the University of Wisconsin's proposed criterion]?

However, CMS' analysis of key set of studies misinterprets the standard that was used in those studies. CMS begins with Grant's 1999 study which reports that programs that have performed at least 10 transplants have significantly higher graft survival rates. The agency then cites Grant's 2003 Intestinal Transplant Registry analysis indicating that centers that have performed 10 transplants compared to those that have performed less than 10 had better results, and then states that this finding was similar to the earlier analysis by Grant in 1999, which was considered in developing the current coverage policies. Yet, CMS continues to miss the point of both Grant's 1999 and 2003 Intestinal Transplant Registry analyses – namely both studies reiterate that a *total* volume of 10 or greater transplants and *not a volume of 10 per year* is associated with improved results.

CMS' review of other studies does not report: whether the study uses 10 annual or 10 cumulative transplants in its analysis; whether the study responds to the question asked; or whether the study's findings actually support the University of Wisconsin's proposed criteria. For example, CMS notes that Langnas' (2004) study did not report on center volume, but still cites the study. CMS also cities the American Gastroenterological Association's review on intestinal transplants, using Intestine Transplant Registry (ITR) data, that found survival at 1 and 5 years was superior at centers that had performed greater than 10 transplants (although these findings were not supported by the UNOS registry data), but the agency does not state whether the authors used 10 annual or 10 cumulative transplants in their analysis.

CMS also cites studies that simply do not address the question the agency poses. CMS cites studies performed by Tzakis (2005), Nishida (2002), and Abu-Elmagd (2001) and states that each of these studies show that centers with high volumes of "close to or more than 100 total transplants over several years had better survival rates than reported from the International Intestinal Transplant Registry." The agency also states that the Middleton study which found one-year survival rates were lower in low volume centers (14 total from 1991-1999) reinforces their concerns about low volume centers. Yet, none

of these studies address the question of relevance here: what is the difference in patient survival between centers that perform 10 transplants annually and 10 transplants cumulatively?

Rather, CMS engages in arguably creative math. The agency concludes, based on a finding that there is more evidence on survival at centers that have performed 100 or more cumulative intestinal and multivisceral transplants, that because these numbers were collected over a period of several years, it must follow that that they represent, on an annual basis, a volume of 10 or more cases per year." There is absolutely no basis or substantiation for such a statement. Yet the agency uses this invented conclusion or these literally made up annual numbers to support its decision to retain its annual volume requirement

When CMS refers to the study by Moon and Tzakis (2004), the agency also fails to note that the results of centers that have performed more than 100 transplants are not better, and in some cases, are actually worse. If one reviews the 2003 International Intestinal Transplant Registry, the one year patient and graft survival for intestinal transplant alone, liver-intestinal transplantation, and multivisceral transplantation are as follows: 77%/65%, 60%/59%, and 66%/61%. If one reviews the University of Pittsburgh's 2001 study published in the Annals of Surgery, the graft survivals in intestinal transplant alone, liver-intestinal transplantation, and multivisceral transplantation are 68%, 63%, and 55%, respectively. There is essentially no difference in graft survival in the intestinal transplant alone as well as liver-intestinal transplantation categories and, in fact, in the Pittsburgh experience, graft survival in their multivisceral transplant experience is lower. In another article, not referenced in this analysis, which is authored by Tzakis *et al.*, (Annals of Surgery Vol 42, No 2, 480493) the authors report on 100 multivisceral transplants at a single center and the l-year patient and graft survival in this series is 65% and 63%, respectively, which compares to 66% and 61% in the International Intestinal Transplant Registry, essentially no difference.

In a 2002 Journal of Gastrointestinal Surgery article, Moon and Tzakis (2004) also refer to another series of 95 intestinal transplants in which they found that the patient and graft survival at 1 year for liver-intestinal transplantation is 40% and 37%, respectively, and for multivisceral transplantation is 48% and 44%, respectively. The results of intestinal transplant alone in this series prior to 1998 was 64% and 63%, respectively. However, CMS chooses to selectively quote only the intestinal transplant alone patient and graft survivals after 1998 in a group of 16 patients which were reported at 84% and 72%, respectively. It is clear in this study that the results of this center are worse for liver-intestinal and multivisceral transplantation and at best equal to the results of the International Intestinal Transplant Registry for intestinal transplant alone. Also, the study by Moon and Tzakis cites the UCLA experience in 2001 when they refer to centers that have done 100 intestinal transplants. However, this series only reports on 21 intestinal transplants and although the reported results are satisfactory, the l-year patient survival of 65% and l-year graft survival of 55% is not different from that of the International Intestinal Transplant Registry.

None of these data support CMS' contention that transplant centers performing more than 100 intestinal transplants in total have significantly better results than transplant centers performing less. In fact, one study from 2004 by the SRTR actually reports that centers performing between 2 and 7 transplants per year had *better* outcomes than those performing 8 or more, indicating that intermediate-sized centers can achieve comparable patient and graft survival rates. Yet, CMS chooses to ignore this study.

CMS also cites studies that have no bearing on the question asked. On page 2 in the Background section, the agency refers to a study by Hosenpud (1994) which demonstrated that greater than 9 *cardiac* transplants a year was associated with decreased mortality and an article by Edwards (1999), which is more appropriate for liver transplantation, and indicates that less than 20 *liver* transplants per year was associated with decreased survival. In terms of liver transplantation, the University certainly would seem to be qualified since it performs 85 to 100 liver transplants per year. However, it seems arbitrary and not clinically legitimate to extrapolate the volume for cardiac or liver transplantation to intestinal transplantation. In fact, CMS basically admits this when it notes that they could not find any studies on mortality and morbidity that directly compared centers based on the number of procedures per year.

CMS also fails to note or acknowledge one of the studies it cites actually supports the University's position that cumulative volume of 10 transplants should be the standard. In CMS' assessment of a series of studies and reports conducted between 2003 -2005, it notes CIGNA's decision to not include volume requirements for coverage of these transplants despite CIGNA's general statement that number of procedures performed was one of three factors significantly associated with patient volume. CIGNA's coverage decision actually supports the University of Wisconsin's position.

When CMS refers to a 2005 study by Middleton and Jamieson, which states that the center that had performed more than 9 transplants had better outcomes, again, they point to a total volume of more than 9 or more *cumulative* transplants, which is what the University has been arguing all along.

CMS also summarizes two sets of public comments; however, it does not present the evidence that the University of Wisconsin submitted on more recent analyses to support its position for using 10 cumulative transplants in setting the standard for transplant center approval. The agency's selective use of data must be challenged - for example, CMS fails to refer to the University of Wisconsin's subsequent challenge to the data cited by the second commenter, Dr. Abu-Elmagd - namely, that a closer analysis of the data the second commenter presented actually substantiates and supports the University of Wisconsin's request.

Other parts of the agency's analysis also fail to respond to the question at issue. For example, CMS concludes that newer medications and advances in surgical techniques, along with improvements in patient and graft survival also support its decision to retain the annual volume requirement. If the issue is one of annual volume vs. cumulative volume, is the agency saying that transplant centers that perform less than 10

transplants per year are somehow deficient in terms of their use of newer medications and surgical techniques, or cannot demonstrate improved patient and graft survival? If so, CMS may want to reconsider that conclusion in light of the fact that some of the transplant centers that CMS approved on the basis of its existing standard of 10 transplants per year have not performed that number of transplants every year since they were approved.

Interestingly, CMS notes that on February 4, 2005, the agency proposed new conditions of participation for the approval and re-approval of Medicare transplant centers and that when these standards become final, there will no longer be national coverage determination transplant center criteria, only approval through a certification process that will be outlined in the Final Rule. The Final Rule is expected to be published in early 2007. However, the agency does not acknowledge that the proposed rule eliminates the 10 annual criteria as well as patient survival criteria entirely. How is the proposed rule, scheduled to become final one year from now, consistent with CMS' statement in this proposed decision memo that "it is important to establish some volume criterion in light of the mortality and morbidity associated with intestinal transplantation." What importance does volume have in 2006 that it will not have in 2007 when the final rule eliminating volume as a criterion is expected to be published?

As we have stated previously, the University is able to meet the criteria of the proposed revised standard with 18 total transplants and a 67% one year patient survival rate. The revised rule that the University is proposing would be fully consistent with CMS' commitment in the Proposed Rule to "focus on an organ transplant center's ability to perform successful transplants and deliver quality patient care as evidenced by good outcomes and sound policies and procedures." 70 Fed. Reg. 15264. The revised rule would also address pressing public policy considerations that strongly support the expansion of Medicare coverage of intestinal and multi-visceral transplants, including improving patients' access to transplant centers in the upper Midwest.

We respectfully request that CMS redo its analysis to reflect the studies cited here as well as accurately reflect the conclusions and data in studies previously cited by the University of Wisconsin and others. We strongly urge CMS to issue a final decision memo that accepts the standard of 10 or more *cumulative* transplants with a one-year patient survival rate of 65 percent which is consistent with available clinical literature. If you have any questions or would like to discuss our analyses of the studies referenced above, please contact me at 608-263-2527 or Martha Kendrick at 202-457-6520.

Sincerely,

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