DEPARTMENT OF HEALTH & HUMAN SERVICES

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September 28, 2000

George R. Newkome, Ph.D.
Vice President for Research
University of South Florida
4202 East Fowler Avenue, ADM 200
Tampa, Florida 33620-5950

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1284

Research Projects: Studies Involving the Tampa Trephine Penetrating Keratoplasty Procedure for Corneal Transplantation
Principal Investigator: J. James Rowsey, M.D.

Dear Dr. Newkome:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your December 16, 1999 report regarding the use of the Tampa Trephine in corneal transplant surgery under the direction of Dr. J. James Rowsey. OHRP has also reviewed your January 12, 2000 follow-up letter that provided the results of the Food and Drug Administration's review of this matter.

In reviewing the documents submitted to OHRP by the University of South Florida (USF), OHRP notes the following:

(1) The October 20, 1994 Task Order #3 Rapid Start Program Technology Deployment Center Grant Proposal entitled "Tampa Bay Trephine" (Principal Investigator: Dr. Rowsey) included the following statements:

(a) "The current method of corneal transplantation involves securing the donor cornea into position with multiple sutures. . . . The Tampa Bay Trephine (working prototype) is a new method of trephining donor corneal tissue which allows us to secure the donor cornea within the recipient bed rapidly and with fewer sutures. . . . We have had preliminary success establishing the surgical protocol by utilizing an eye bank eye model developed here at USF."

(b) "The initial feasibility studies will be accomplished at the USF Department of Ophthalmology. We believe that the feasibility study is three fold. . . . Prior to

commencing any live animal studies to test the new trephine, one needs to know the reproducibility and precision of the device. We anticipate this can be accomplished in an in-vitro experiment. . . .This question can be answered by simply punching 20 donor corneas and measuring tissue."

(c) "The next phase of the study will be to develop and refine surgical technique in a live animal system prior to human use. We would use the cat as a surgical model as the cat ocular anatomy closely resembles the human."

(d) "The next preliminary phase to be accomplished at USF will be a comparison study assessing postoperative recovery in the cat eye which receives a penetrating keratoplasty with the Tampa Bay trephine versus the traditional method which uses the Weck trephine."

(e) "Upon initial results of the second cat study, human use of the trephine will be initiated by Dr. J. James Rowsey and his associates . . . ."

(2) The USF Institutional Animal Care and Use Committee (IACUC) Request for Use of Animals entitled "Refinement & Development of Tampa Bay Trephine Surgical Technique in the Cat" (IACUC File #1049) submitted by Dr. Rowsey on July 18, 1994 included the following statements:

(a) "The purpose of this experiment is to refine the surgical technique of corneal transplantation using the Tampa Bay Trephine in a live model."

(b) "The Tampa Bay Trephine is being developed for human use and a live model for in-vivo testing is necessary prior to human use."

(3) The USF IACUC Request for Use of Animals entitled "Comparison Study Assessing Post-Operative Recovery in Cats which Receive a Penetrating Keratoplasty with the Tampa Bay Trephine versus the Traditional Method Utilizing the Weck Trephine" (IACUC File #1048) submitted by Dr. Rowsey on July 18, 1994 included the following statements:

(a) "Development of a new trephine method which allows for no sutures has many potential benefits including but not limited to less corneal astigmatism, more rapid recovery of post-operative visual acuity, and decreased incidence of graft rejection."

(b) "The Tampa Bay Trephine is being developed for human use and a live model for in-vivo testing is necessary prior to human use."

(4) The informed consent document for Dr. Rowsey's proposed randomized clinical trial entitled "Assessment of Post-Operative Healing Time and Induced Astigmatism when

Penetrating Keratoplasty is Performed Using the Tampa Trephine Versus the Traditional Weck Trephine" that was approved by the IRB on June 5, 1995; July 8, 1996; and June 2, 1997 (IRB protocol #3877), stated the following:

> (a) "You are being asked to consent to and participate in a study designed to evaluate the safety and effectiveness of the Tampa Trephine, a new surgical device that enables the surgeon to perform a corneal transplant with less sutures, which may result in faster healing time and possibly less astigmatism. *The Tampa Trephine is an investigational device and the stability of postoperative results has not been established.*" [Italics added for emphasis.]
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> (b) "A preclinical study to evaluate this procedure for corneal transplants has been performed safely in animal models. The beneficial results and possible risks of this treatment in sighted patients however, are not completely known. This will be the first limited trial of the Tampa Trephine procedure for sighted patients."
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> (c) The ALTERNATE PROCEDURES OR TREATMENTS section of the informed consent document indicates that one of the alternatives to participating in the research is to undergo "a routine corneal transplant." Undergoing the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation was not listed as an alternative procedure available outside the research context.

(5) Continuing review progress reports for IRB protocol #3877 indicate that no subjects were ever enrolled in this randomized clinical trial.

(6) Dr. Rowsey and his colleagues drafted and/or submitted a series of abstracts and manuscripts to scientific meetings and peer reviewed scientific journals describing an ever increasing sample size of individuals who had undergone the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation, as well as data on the outcomes and adverse events associated with the procedure including detailed serial measurements of visual function and ocular anatomy. Selected excerpts from these abstracts and manuscripts include the following:

> (a) Rowsey JJ, Stevens SX, Fouraker BD, Polack PJ, Sanchez JC, Tsal JC, Young DA. Tampa Trephine: A New Tissue Tab Technique for Corneal Transplantation-The First Human Cases (an abstract published in the Final Program of the 1995 American Academy of Ophthalmology Annual Meeting, Atlanta, Georgia, Oct. 29-Nov 2, and scheduled to be presented at a Thrusday Scientific Session at 2:20 PM):
>
> > "We report the first four cases using the Tampa trephine (TTPK). ***Methods:*** Prospective evaluations including preoperative conditions, intraoperative events and early post operative outcomes (vision, IOP, pachymetry, and topography) were performed. . . . ***Conclusions:*** TTPL is a safe technique. Early results suggest a more rapid wound healing."

(b) Rowsey JJ, Fouraker BD, Stevens SX, Sanchez-Thorin JC, Rocha G. Tampa Trephine Penetrating Keratoplasty: Preliminary Patient Insights (an undated manuscript):

(i) "Presented at the American Academy of Ophthalmology Annual Meeting, Atlanta, Georgia, November 1995."

(ii) "Abstract: . . . We report results from the first eleven patients operated with this technique. . . ."

(iii) "PATIENTS AND METHODS . . . All patients eligible for surgery during the time period between March and May 1995 were included in the study. . . ."

(iv) "Data was collected prospectively both preoperatively and over a two month postoperative period. Computerized corneal topography using the EyeSys Corneal Analysis System . . . was performed at several time points postoperatively."

(c) Rowsey JJ, Sanchez-Thorin JC. Rocha G, Stevens SX, Duplessie M, Fouraker B, Michaelos J. Tampa Trephine Penetrating Keratoplasty: Preliminary Patients Insights (an undated manuscript):

(i) "Presented at the American Academy of Ophthalmology Annual Meeting, Atlanta, Georgia, November 1995."

(ii) "**ABSTRACT** . . . . **Background and Purpose**:. . . . We report the preliminary results from the first sixteen patients receiving this technique with a two month follow-up period. . . ."

(iii) "**PATIENTS AND METHODS** . . . . Patients included in this report provided a minimum two month postoperative period. . . ."

(iv) "Data was collected prospectively both preoperatively and postoperatively, and included uncorrected and best corrected visual acuity, refraction, ultrasonic pachymetry . . ., intraocular pressure . . ., a slit lamp examination, and computerized corneal topography(CCT) using the EyeSys Corneal Analysis System. Examinations were performed preoperatively and one day, one week, two weeks, four weeks, and then monthly in the postoperative period."

(d) Rowsey JJ, Sanchez-Thorin JC. Rocha G, Stevens SX, Duplessie M, Fouraker B, Michaelos J. Tampa Trephine Penetrating Keratoplasty: Preliminary Patients

Insights (an undated manuscript apparently submitted to Ophthalmology in late 1995 or early 1996).

(i) "Presented at the American Academy of Ophthalmology Annual Meeting, Atlanta, Georgia, November 1995."

(ii) "**ABSTRACT** . . . . **Purpose**: We report the preliminary results from the first sixteen patients receiving this technique with a three month follow-up period. . . ."

(iii) "**PATIENTS AND METHODS.** Patients eligible for surgery were aged 6 to 85 years . . . . Patients included in this report were required to have a minimum three month postoperative period. . . . Data was collected prospectively both preoperatively and postoperatively, and included uncorrected and best corrected visual acuity, refraction, ultrasonic pachymetry . . ., intraocular pressure . . ., a slit lamp examination, and computerized corneal topography . . .using the EyeSys Corneal Analysis System. Examinations were performed preoperatively and one day, one week, two weeks, four weeks, and then monthly in the postoperative period."

(e) Rowsey JJ, Sanchez-Thorin JC, Rocha G, Stevens SX, Fouraker B, Duplessie M, Michaelos J. Penetrating Keratoplasty Utilizing the Tampa Trephine (an abstract presented at the World Congress of Cornea IV, Orlando, Florida, April 17-19, 1996):

(i) "In theory TTPK offers some advantages over standard penetrating keratoplasty. . . ."

(ii) "Purpose: To report a case series of 41 patients who underwent TTPK with a minimal follow-up period of four months.

(iii) "Methods: . . . . Patients were prospectively evaluated through routine eye examinations including ultrasonic pachymetry and computerized corneal topography."

(f) Rowsey JJ, Sanchez-Thorin JC, Maglione A, Rocha G, Fouraker B, Stevens SX. Tampa Trephine Penetrating Keratoplasty: Results of the First 35 Cases (an undated manuscript):

(i) "Presented at the World Congress of Cornea IV, Orlando, Florida, April 17-20, 1996."

(ii) "ABSTRACT . . . . Methods: Thirty five patients were submitted to TTPK and evaluated postoperatively at days 1, 7, and 15, and months 1, 2, 3, and 4. Retrospective evaluations for this study included visual acuity, computerized corneal topography, ultrasonic pachymetry, slit lamp examination and intraocular pressure."

(iii) "Conclusions: Tampa Trephine penetrating keratoplasty is a viable surgical technique offering potential theoretical benefits and risks over the standard penetrating keratoplasty technique. A comparative assessment of risks and benefits needs to be addressed through randomized clinical trials."

(g) Moura RC, Stevens SX, Rowsey JJ. Tampa Trephine Penetrating Keratoplasty: One year follow-up (an undated manuscript; given dates of surgical procedure and the time range for postoperative follow-up, this must have been prepared on or after October 1996)

(i) "ABSTRACT: PURPOSE: We analyzed the one year follow-up results of 51 consecutive eyes that underwent corneal transplantation with the Tampa Trephine (1). METHODS: Thirty-four eyes of thirty-four patients satisfied our inclusion and exclusion criteria and were included in this study. Visual acuity, manifest refraction, corneal pachymetry, intraocular pressure, and corneal topography results were assessed. RESULTS: The mean follow-up was 11.88 months (from 10 to 14 months). . . . CONCLUSION: The Tampa Trephine technique is safe and stable. Results didn't differ from the standard PK. . . ."

(ii) "DISCUSSION. . . .We compare our results to the current literature and verify several variables that can affect final visual acuity. . . ."

(iii) "CONCLUSIONS. . . . More studies have to be done in order to get the best of this new technique."

(h) Rowsey JJ, The Tampa Trephine Study Group. Tampa Trephine Penetrating Keratoplasty: A Tissue-Tab Technique for Corneal Transplantation (book chapter published in 1997 *International Ophthalmology Clinics)*:

(i) "In theory, the presence of these tabs [on the donor cornea harvested with the Tampa trephine], when amalgamated to the recipient donor tissue, may allow for a more stable host-donor interface."

(ii) "Initial results of patients operated with this technique have been presented (American Academy of Ophthalmology, Atlanta, GA, October 31, 1995; World Congress of Cornea, Orlando, FL, April 17, 1996, submitted for publication)."

(iii) "The following are important concerns with the Tampa trephine PK technique:

> "Inadequate handling of the donor material can damage the donor endothelium. . . . Donor epithelium on the tabs can produce loculated epithelial inclusion cysts in the recipient stroma. This can favor corneal neovascularization and, eventually, increase the risk of a graft rejection. . . . The proximity of the recipient Langerhans' cells to the donor tab tissue may increase the risk for graft rejection . . . . Microorganisms may loculate in the stromal pockets, including a localized abscess in the recipient bed."

(iv) "The Tampa trephine PKP may prove to be a successful technique, achieving its theoretical potential advantages. Further clinical trials are necessary to establish the efficacy of this procedure as compared to the standard PKP technique."

(7) In a March 22, 1999 letter to Dr. Martin Silbiger, Vice President of Health Sciences, College of Medicine, USF, Dr. Rowsey stated the following:

> "On page 8, the Committee states, 'It is the opinion of this committee that these determinations constitute at the very least an informal comparison of outcome regarding Tampa Trephine keratoplasty versus standard penetrating keratoplasty, and serve to reinforce the need for compliance with 45 CFR 46.' What actually occurred was that I performed an 'observational study' with 'informal comparisons' documented daily, based on patient follow-up. I fully described my findings in the manuscripts cited by the Curran Committee."

(8) The USF Final Report of the Investigation Panel, dated October 21, 1999, included the following statements:

> (a) "[T]he clinical use of the Tampa Trephine device should have been the object of formal research at an early stage in order to determine whether it was safe and effective. The panel believes that this is particularly important in light of the fact that this was an investigative procedure."
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> (b) "Dr. Rowey did not make accurate and complete disclosures to the USF IRB in 1995. . . . He over-represented the safety and efficacy of the Tampa Trephine to the IRB, and misled the IRB by implying that this was not a new technique requiring special informed consent."
>
> (c) "Dr. Rowsey should have informed all of his Tampa Trephine patients that they were going to undergo an investigative procedure."

(d) "Our review of the evidence, including the medical records [of patients undergoing the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation], indicates significantly more complications than are normally found when using standard techniques."

(9) The Final Report of the University of South Florida Standing Committee on Research Misconduct (SCRM), dated 14 December 1999, included the following statements:

(a) "Beginning in February, March, or April 1995, Dr. Rowsey initiated use of the Tampa Trephine in relation to patient care. The large majority of these patients were treated at Tampa General Hospital. Note that use of the Tampa Trephine in relation to patient care was initiated during the first *in vivo* cat experiment, and a full year prior to commencement of the second cat experiment."

(b) "It is also noted that use of the Tampa Trephine device necessitated a significant departure from standard corneal transplant technique, and therefore introduced unknown risks and uncertain efficacy."

(c) "It is the conclusion of the SCRM that Dr. Rowsey demonstrated poor judgement in how he distinguished between his clinical and research practices regarding use of the Tampa Trephine and its associated keratoplasty technique."

(d) When he initiated use of the differently cut corneas in patient care, Dr. Rowsey had high expectations for the performance of his innovative approach. Although most of these expectations were never formalized in designed research studies, the SCRM agrees that these expectations were equivalent to informal statements of hypothesis."

(e) "*The SCRM unanimously agrees with the second conclusion of the Investigation Panel, in that after the first few patients, Dr. Rowsey's work should have become the subject of a formal research study.*"

(f) "We note that in contrast to previous trephines, the Tampa Trephine required major modifications to the surgical procedure."

(g) "If on the other hand both animal studies were indeed necessary prior to commencement of use of the Tampa Trephine in clinical contexts as originally argued, the fact that the new approach was used in humans prior to conclusion of either animal study, and even prior to any preliminary results being available from the second, is even more disconcerting to the SCRM."

OHRP Findings

Based on its evaluation of the above referenced documents, OHRP makes the following determinations:

(1) The Tampa Trephine penetrating keratoplasty procedure for corneal transplantation significantly departed from the standard corneal transplant procedure and introduced unknown risks and uncertain efficacy. In particular, the Tampa Trephine penetrating keratoplasty procedure significantly altered the morphology of the harvested donor cornea and the surgical procedure for implantation of the donor cornea in the transplant recipient.

(2) The Tampa Trephine penetrating keratoplasty procedure for corneal transplantation had never been attempted in humans prior to Dr. Rowsey's use of the procedure.

(3) At least 60 humans patients underwent the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation between approximately March 1995 and March 1998.

(4) Department of Health and Human Services (HHS) regulations at 45 CFR 46.102(d) define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. HHS regulations at 45 CFR 46.102(f) defines human subject as a living individual about whom an investigator conducting research obtains (i) data through intervention or interaction with the individual; or (ii) identifiable private information.

OHRP finds the activities involving the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation under the direction of Dr. Rowsey unequivocally represented research involving human subjects. In specific, OHRP finds that:

(a) Dr. Rowsey and his co-investigators systematically and prospectively collected data regarding the safety and effectiveness of the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation using an open-label, non-randomized, single-treatment-arm pilot study.

(b) The Tampa Trephine penetrating keratoplasty procedure represented a research intervention that had undergone only limited preclinical testing in animal studies which had not been completed prior to Dr. Rowsey's initiation of this research on human subjects.

(5) HHS regulations at 45 CFR 46.109(a) and the USF MPA (see Part 1, section II.B) require that all research involving human subjects that is not exempt be reviewed and approved by the IRB.

OHRP finds that the human subject research involving the open-label, non-randomized, single-treatment-arm pilot study of the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation was conducted without IRB review and approval.

(6) HHS regulations at 45 CFR 46.102(i) stipulate that *minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

OHRP finds that the human subject research involving the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation involved greater than minimal risk.

(7) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that in order to approve research the IRB shall determine that risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result.

OHRP finds that because the IRB failed to review and approve the human subject research involving the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation, these regulatory requirements were not satisfied.

(8) HHS regulations at 45 CFR 46.116 stipulate that no investigator may involve a human subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

OHPR finds that the human subject research involving the Tampa Trephine penetrating keratoplasty procedure was conducted without the investigators obtaining the legally effective informed consent of the subjects or the subjects' legally authorized representatives.

(9) HHS regulations at 45 CFR Part 46, Subpart D stipulate additional protections for children involved as subjects in research. OHRP finds that:

(a) The human subject research involving the Tampa Trephine penetrating keratoplasty procedure involved children as subjects.

(b) In its MPA, USF assured OPRR that the additional safeguards stipulated by 45 CFR Part 46, Subpart D would be implemented for all research involving children, regardless of sponsorship (see Part 1, sections II.A and III.A; and Part 2, section I.B).

(c) The children participating in the human subject research involving the Tampa Trephine penetrating keratoplasty procedure were not afforded the additional protections stipulated by HHS regulations at 45 CFR Part 46, Subpart D.

OHRP acknowledges that (i) the Tampa Trephine penetrating keratoplasty procedure for corneal transplantation is no longer being used by investigators at USF or its affiliated institutions; and (ii) Dr. Rowsey no longer works at USF.

Required Actions:

In view of the above findings, OHRP requires that USF take the following actions:

(1) One of the USF IRBs responsible for oversight of biomedical research must develop a plan, including both the means and the content, for contacting all surviving subjects (or the parents or legal guardians of children who were subjects) who participated in the human subject research involving the Tampa Trephine penetrating keratoplasty procedure and informing them of their previous unwitting participation in the research, the risks associated with the research, and the nature of the noncompliance by USF with the requirements of HHS regulations at 45 CFR Part 46. Please submit to OHRP a written report regarding the IRB's determinations and plan for this matter and the documentation underlying these determinations, including relevant IRB minutes and the proposed text for debriefing the surviving subjects (or the parents or legal guardian of children who were subjects). Please forward your report so that OHRP receives it no later than October 31, 2000.

(2) USF, in conjunction with all of its investigators and clinical practioners, as well as relevant administrators, must audit and identify all on-going research projects involving human subjects that is not exempt under HHS regulations at 45 CFR 46.101(b) and confirm that all such research has been reviewed and approved by one of USF's IRBs. USF must suspend immediately any nonexempt research involving human subjects that has not been reviewed and approved by one of USF's IRBs. By October 31, 2000, please provide OHRP with a report on the results of this audit and a list of any research activities that have been suspended as a result of this audit.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Chief, Compliance Oversight Branch
Division of Human Subject Protections

cc: Dr. Barry B. Bercu, Chairperson, IRB-01/02, USF
Dr. Martin Klemperer, Chairperson, IRB-03, USF
Dr. William B. Webster, Chairperson, IRB-04, USF
Dr. J. James Rowsey
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
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