RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer”

Study Chair: Lawrence B. Berk, MD, PhD, 813-844-7585, lberk@health.usf.edu

RTOG 1012 has been amended as follows:

Title page: This amendment was added to the Document History table.

Eligibility Checklist: Question 4 on page 1 was added to be consistent with the addition of Section 3.1.4.

Section 3.0: The 2nd sentence was added to update this section to current RTOG standard text.

Section 3.1.4 was added, requiring that patients speak English or Spanish in order to complete the mandatory EORTC QLQ-30 and PRO-CTCAE, which are only available in certain languages. The subsequent section was appropriately renumbered.

Section 4.1.3: A parenthetical phrase was added to provide sites with instructions regarding translating the NRPS and swallowing diary for Spanish speaking patients.

Sections 5.1.1 and 5.1.2 were updated to current RTOG standard text.

Section 7.3: The link to the Material Safety Data Sheet was corrected.

Section 7.3.2: In the 3rd paragraph, the 2nd sentence was amended, as the exact quantity of honey (jars and blister cards of lozenges) shipped is determined by communication between the site and the distributor.

Section 7.3.4: Two changes were made for clarity:
- In the 1st paragraph, the 2nd sentence was added.
- In the 3rd paragraph, the 1st sentence was amended.

Sections 7.6, 7.6.1, and 7.6.2 were updated to current RTOG standard text.

Section 7.6.3 was updated to current NCI standard text.

Section 7.7: Four paragraphs and a bulleted list were added to update this section to current RTOG standard text.

Section 11.2.4.2 was added to provide instructions for a patient survey to assess the patient’s satisfaction with and the usability of the PRO-CTCAE system.

Section 12.1:
- Under “Due”, the timeframe for the NRPS (QP), PRO-CTCAE, and Swallowing Diary (DP) was amended.
- Under “Due”, a reference was added directing sites to Section 11.2.4.2 for the submission time point for the Patient Survey.

Section 13.4.2.5:
- The 2nd sentence, regarding the time points for the PRO-CTCAE, was added.
- The 2nd paragraph was added to be consistent with the addition of the patient survey in Section 11.2.4.2.

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Appendix I: Under “What will happen if I take part in this research study?” and “During the study”, the last bulleted item, regarding the Patient Survey, was added to be consistent with the addition of Section 11.2.4.2.
RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer”

Study Chair: Lawrence B. Berk, MD, PhD, 813-844-7585, lberk@health.usf.edu

RTOG 1012 has been updated as follows:

Section 7.3.4: The 1st paragraph was updated with the correct storage temperature for liquid (jarred) honey.

Section 11.2.4.1: The 2nd paragraph was updated with a direct link to the CRA Survey.
SUMMARY OF CHANGES
Amendment 3, Version: January 30, 2013

RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer”

Study Chair: Lawrence B. Berk, MD, PhD, 813-844-7585, lberk@health.usf.edu

RTOG 1012 has been amended as follows:

Title page: The Senior Statistician’s last name and e-mail address were updated. In addition, this amendment was added to the Document History table.

Section 7.3.4: In the 3rd sentence of the 2nd paragraph, “99.75%” was replaced with “primarily”. The percentage of honey in some lozenges may vary due to the inclusion of a new additive that reduces melting. The variance in percentage of honey does not affect the dose described in Section 7.2.3.
SUMMARY OF CHANGES
Amendment 2, Version: November 14, 2012

RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer”

Study Chair: Lawrence B. Berk, MD, PhD, 813-844-7585, lberk@health.usf.edu

RTOG 1012 has been amended as follows:

Title page: Dr. Basch’s affiliation and contact information was amended. In addition, this amendment was added to the Document History table.

Index page: Appendix XI was deleted, as sites now can access the PRO-CTCAE Materials on the RTOG web site.

Section 5.5.5.2: Dr. Basch’s e-mail address was amended.

Section 7.3: The 1st paragraph was added to tell sites that there is no Investigator Brochure for honey and to refer sites to comparable information on the Material Safety Data Sheet posted on the RTOG web site.

Section 7.3.2: The first 3 paragraphs were amended to reflect that the distributor of Manuka honey has changed from Catalent Pharma Solutions to Biologics, Inc. In addition the shipment schedule was amended and 3 paragraphs were added below the table. Finally, the contact information for questions about supply and delivery was amended.

Section 7.3.4 was amended to provide more complete information about the storage and stability of the liquid and lozenge form of honey.

Section 11.2.4: The last sentence of the 1st paragraph was amended to direct sites to the RTOG web site for the “Missed Login Form”.

Section 11.2.4.1: In the 2nd paragraph, the phrase, “after the first”, was repeated unnecessarily. This error was corrected. In addition, the last sentence of the section was amended to reflect a new process in which CRAs will complete the survey using an online survey site.
RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer”

**Study Chair:** Lawrence B. Berk, MD, PhD, 813-844-7585, lberk@health.usf.edu

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**RTOG 1012** has been updated as follows:

**Section 7.3.4:** The storage temperature for the Manuka honey lozenges was corrected from “above 65 degrees Fahrenheit” to “below 65 degrees Fahrenheit.”
RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer"

Study Chair: Lawrence B. Berk, MD, PhD, 813-844-7585, lberk@health.usf.edu

RTOG 1012 has been updated as follows:

Title page: The “Version Date” was deleted to amend the protocol to the current RTOG standard of bolding the version date of the protocol in the Document History table. In addition, this update was added to the Document History table.

Section 7.3.4 was updated to clarify the storage of the liquid and lozenge forms of Manuka honey.
SUMMARY OF CHANGES
Amendment 1, Version: June 28, 2012

RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer”

Study Chair: Lawrence B. Berk, MD, PhD, 813-844-7585, lberk@health.usf.edu

RTOG 1012 has been amended as follows:

Title page:
- Dr. Berk’s affiliation and contact information were updated.
- Dr. Basch’s fax number was updated.
- The sentence, “This trial is open to U.S. institutions only”, was added for clarity and for consistency with Sections 5.0 and 7.0.
- “Study Chairs” was amended to “Study Team” to reflect the current RTOG standard text.
- This amendment was added to the Document History table.

Section 1.4:
- In the 2nd paragraph, “10 ml” was amended to “10 cc” for consistency.
- The last sentence was corrected to say that patients will refrain from eating 1 hour after swallowing the honey to be consistent with Section 7.2 and Appendix I.

Section 5.2.1:
- The link to the CTSU-IRB Certification Form was updated.
- “REB” was deleted throughout the section, as the study is available to U.S. institutions only.

Section 5.3: In the 2nd bulleted item of the 2nd paragraph, the link to the Password Authorization Form was updated.

Section 7.2.1: The last sentence regarding use of sucralfate was deleted, as supportive care is addressed in Section 9.0.

Section 7.3: RTOG holds the IND for the study, and the IND number was added to the heading.

Section 7.3.1:
- In the 2nd paragraph, “10 ml” was amended to “10 cc” for consistency.
- In the 3rd paragraph, the first sentence referring to “a single lot” was deleted and in the 4th sentence, the phrase, “of the lot” was deleted, as more than 1 lot of honey may be needed for the study.

Section 7.3.2
- The 1st paragraph was amended to indicate that RTOG holds the IND for the study.
- The name of the distributor of Manuka honey, “Aptuit, Inc.” was updated to “Catalent Pharma Solutions” throughout the section.

Section 7.3.5: The phrase, “burning of the mouth or esophagus”, was clarified to “a sensation of burning of the mouth or esophagus.”

Section 7.6.2: The last sentence of the 2nd paragraph was amended to current RTOG standard text.

Section 7.7: in the 2nd paragraph and in the 1st footnote of the table, the phrase, “under a non-CTEP IND” was added to be consistent with RTOG holding the IND for the study.

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Section 9.1.3 was added to clarify that patients may take nutritional supplements, such as Ensure®.

Section 9.4.1: The phrase, "such as molasses or thick maple sugar", was added to the 2nd paragraph for clarity.

Section 11.2.4.1: The fax number of the PRO-CTCAE Project Manager was updated.

Section 13.4.1: In the last paragraph, the last sentence was added to clarify the statistical analysis.

Section 13.4.2.6 was added to provide the statistical analysis for the dysphagia endpoint (Section 13.1.2.2)

The following changes were made in Appendix I:
- Under "Before you begin the study?", the phrase, "such as molasses or thick maple syrup", was added to the last paragraph for clarity.
- Under "Risks and side effects to Manuka honey", the Less Likely risk of "burning of the mouth or esophagus", was amended to "A feeling of burning of the mouth or esophagus" for clarity.
- Under "Will my medical information be kept private?", in the 2nd paragraph, the Active Manuka Honey Association was removed as an organization that may access patients' information. Data and serious adverse events will not be reported to this organization.
- Under "Where can I get more information?", the TTY number was deleted at CTEP's request.

The following changes were made in Appendix XI:
- The PRO-CTCAE Screen Shot was updated.
- In the instructions for the “Missed PRO-CTCAE Login Form”, the grace period was corrected from 2 to 3 days to be consistent with Section 11.2.4.
- In the instructions for the “Missed PRO-CTCAE Login Form”, the e-mail address for the PRO-CTCAE Coordinator was added.
RTOG 1012, “Phase II Randomized Trial of Prophylactic Manuka Honey for the Reduction of Chemoradiation Therapy Induced Esophagitis-Related Pain During the Treatment of Lung Cancer”

Study Chair: Lawrence B. Berk, MD, PhD, 813-745-1622, Lawrence.Berk@moffitt.org

RTOG 1012 has been updated as follows:

Title page: The e-mail addresses of Drs. Basch and Shook were updated. In addition, a “Document History” table was added to update the protocol to current RTOG standards.

Section 1.3.3: In the 3rd sentence of the 1st paragraph, the number of symptoms in the CTCAE was corrected from 80 to 78.

The following changes were made in Section 5.2:
- Due to logistical constraints, the study will be available to U.S. institutions only; therefore, references to and instructions for Canadian and non-Canadian international sites were deleted from Sections 5.2.1 and 5.2.4.1, and Sections 5.2.2, 5.2.3, and 5.2.4.2 were deleted.
- In Section 5.2.1, the link to the CTSU-IRB/REB Certification Form was updated, and the 2nd sentence was added to update the protocol to current RTOG standards.
- In Section 5.2.4.1, the location of the Study Agent Shipment Form on the RTOG website was updated. This change also was made in Section 7.3.2.
- In the 2nd paragraph of Section 5.2.5.1, the e-mail address was updated.
- In Section 5.2.5.2, Dr. Bruner was removed as a contact for sites. The e-mail address for Dr. Basch was updated, and the e-mail for the PRO-CTCAE coordinators was added.

Section 5.3.1: In the 2nd bulleted item, the link to the Password Authorization Form was updated.

The following changes were made in Section 7.3.2:
- In the 2nd paragraph, the 2nd sentence was added to update the protocol to current RTOG standards.
- In the 2nd and 4th paragraph, references to and instructions for Canadian and non-Canadian international sites were deleted, as due to logistical constraints, the study will be available to U.S. institutions only. In addition, Section 7.3.2.1, referring to non-Canadian international sites, was deleted.
- The 3rd paragraph was updated, and a table was added providing the shipment schedule for the study agent.
- In the last paragraph, contact information for Aptuit was updated.

Section 7.6: In the 3rd paragraph, the link to information concerning serious adverse events was updated.

Section 7.7: The table for AdEERS Expedited Reporting Requirements was updated as required by CTEP.

The following changes were made in Section 11.2.4:
- In the 1st paragraph, the grace period allowed for the patient to complete the self-report was updated from 2 to 3 business days.
- The last sentence was clarified.
- The last paragraph was replaced with Section 11.2.4.1 to clarify details of the Clinical Research Associate Survey.
The following changes were made in Section 12.1:

- The designation for the Swallowing Diary was corrected from “PD” to “DP”.
- Under “Due”, in the schedule for the Cover Sheet for the NRPS, the “PQ form” was corrected to the “QP form”.
- The Follow-up Form (F1) was deleted, as it is unnecessary for this study.

Appendix I: Under “Will my medical information be kept private?”, the last 3 paragraphs were added to update the sample consent to the current NCI consent template.

Appendix XI: The example of a PRO-CTCAE screen shot was updated and Dr. Basch’s e-mail address was updated.