OVERVIEW

These guidelines are provided to assist with the site monitoring and review process for the Philip Morris TESFU study. Detailed instructions for completing the CRFs are included in the CRF binder. This document should be used as a monitoring tool to assure consistency in data handling across centers and will be updated as necessary.

Covance will be responsible for the overall management of this project to include project management, regulatory and enrollment tracking, and data management. MDS will be responsible for statistics and the final report. Is this true Mary? Clinimetrics will be responsible for the monitoring only for this project.

The Investigator Meeting was held on October 8, 2004. All initiation visits are estimated to be done in early November 2004. Enrollment for this project is estimated to end in December 2004. All closeout visits are estimated to be done in January 2005.

CONTACTS

The Clinimetrics CRA will be the first line of communication with the site. Following that:

For all other study specific questions, the site should call:

Covance – Project Manager
Mary Larson
Phone – 608-443-1442
Fax – 608-661-8169

For exemption subject approvals, the site should call:
Covance – Project Manager
Jason Moresco
Phone – 608-443-1436

For all regulatory and contract questions, the site should call:
Covance – Regulatory Manager
Sarah Helgeson
Phone- 608-443-1459
Fax – 608-661-8169

For all other monitoring specific questions, please call:
Clinimetrics – Project Manager
Jenny Camp
Phone – 404-355-6966
Fax – 404-355-6937

CRA Assignments:

First Name	Last Name	San Jose 408-452-8215 Ext.	Phone #	Mobile#	Fax#	State	Zip	Sites
Barb	Ballard	235	503-675-3481	408-425-6806	503-697-3749	OR	97035	Portland OR Billings, MT Missoula, MT Dallas, TX Gainsville, FL St. Louis, MO
Mike	Cui	396	734-434-0548	734-678-6473	734-434-0548	MI	48197	Madison, WI Duncansville, PA Lawrenceville, NJ
Philip	Fabella	217	909-894-2263	N/A	909-894-7522	CA	92563	Phoenix, AZ Las Vegas, NV Oklahoma City, OK Raleigh, NC
Dana	Gordon	313	404-531-0216	404-931-0710	404-531-0216	GA	30342	Atlanta, GA Cincinnati, OH Stuart, FL
Charlie	Peters	397	503-296-8668	971-404-4204	N/A	OR	97225	Edina, MN Fargo, ND Boise, ID Knoxville, TN
Paula	Ballard	180	541-265-9121	541-961-3663	541-265-9331	OR	97365	Back-up CRA
Cherie	Bolasna	460	408-452-8215	408-439-4402	408-452-0912	CA	95138	Back-up CRA

Site Assignments:

SITE NAME	ADDRESS	CITY	STATE	Possible Subjects	ZIP	PHONE #
Covance CRU	3402 Kinsman Blvd	Madison	WI	8	53704	608-443-1443
nTouch	3909 Sunset Ridge #102	Raleigh	NC	8	27607	919/789-9323
Lawrenceville Urology	3120 Princeton Pike	Lawrenceville	NJ	34	08648	609-895-1991
Radiant	6565 W. Emerald St.	Boise	ID	6	83704	208/321-2081
Radiant	5331 SW Macadam Ave. #210	Portland	OR	8	97201	503/294-7193
nTouch	5300 N. Grand Blvd. Suite 300	Oklahoma City	OK	7	73112	405/949-0799
Montana Health	2101 Broadwater Ave.	Billings	MT	7	59102	406/652-6630
NW Physician's Research	700 S Avenue West Ste A	Missoula	MT	7	59801	406/721-5024
Radiant	6039 Eldora Ave. Suite H	Las Vegas	NV	11	89416	702/257-2600
Radiant	5939 Harry Hines Blvd. #441	Dallas	TX	26	75235	214/424-0408
Radiant	1100 Lake Hearn Dr. Suite 360	Atlanta	GA	21	30342	404/255-6005
Radiant	522 N. New Ballas, Ste 350	St. Louis	MO	12	63141	314-692-2100
Radiant	7720 Montgomery Rd.	Cincinnati	OH	16	45236	513/984-6887 x229
University of Tennessee	1928 Alcoa Hwy. Suite G-50	Knoxville	TN	8	37920	865/544-9356
Altoona Center	1125 Old Route 220 North	Duncansville	PA	7	16635	814/693-0300
Radiant	1014 NW 57th St. Suite A	Gainsville	FL	6	32605	352/331-4019
Radiant	2081 E. Ocean Blvd. Suite 1A/3A	Stuart	FL	11	34996	772/781-3000x221
Radiant	333 West Thomas Rd, Suite 100	Phoenix	AZ	7	85013	602-277-9256
Radiant	6545 France Ave. South Suite 290	Edina	MN	11	55435	952/924-5975
PRACS	4801 Amber Valley Parkway	Fargo	ND	11	58104	701/461-8202

RECRUITMENT and ENROLLMENT PROCEDURES

- Covance will send out letters (see study manual) with a self addressed stamped envelop to all subjects that indicated that they would be interested in participating in the trial AND that they have switched to a cigarette tar level at least 3.0mg different from what they smoked in the short term TEST study.
- Covance will be asking that the subject send an empty pack of their current brand of cigarette to them to verify eligibility before their visit 1 appointment. If the subject presents with another type of cigarette, they will be excluded. Sites will be provided with a master spreadsheet indicating the subjects that are eligible at their site.
- The subjects will be instructed to call the sites directly to make an appointment.
- The sites will go through the telephone questionnaire with the subjects to determine if they qualify. Subject MUST smoke a cigarette brand with a tar level of at least 3.0 mg different from their TEST level. This information is located on the master spreadsheet provided by Covance.
- If the subject appears qualified, a visit 1 appointment is scheduled. The time of both visit 1 and visit 2 appointments MUST coincide with the blood draw times listed on the master sheet. The reason for this is that the biomarkers from the TES study will be compared with the biomarkers of this study and the blood draw times MUST be within +/- 3 hours of the blood draw in the TES study.
- When the subject arrives for visit day 1, a copy of the cigarette pack as well as the master list needs to be faxed to 608-661-8169 attn: Mary Larson. As a monitor, all of the above must be verified to include review of the master spreadsheet and telephone questionnaire.

STUDY SUPPLIES / LABORATORY SUPPLIES

- Covance Central Laboratories (CCLS) will provide all laboratory supplies for this project for blood and urine sample analysis. [refer to the Covance laboratory binder for details].
- Contact Linda Heiser at 1-800-327-7270 for all requests and questions regarding laboratory reports.
    - CCLS will fax all laboratory report results within 24 hours of the analysis directly to the site.
- Ensure that each site has the following:
    - Laboratory kits from CCLS
    - Bulk supplies from CCLS to include cooler, ice packs, urine collection kits to
    - 1 liter cylinder to measure 24 hour urines
    - Topography devices (one for each subject)
        - Contact Mark Likness for any topography device questions or concerns at 1-410-342-5947
    - CRF books
    - Regulatory binder

- Logs
  - Master-subject log
  - Enrollment/ screening log
  - Monitoring signature log

MONITORING OVERVIEW

Monitoring will be performed using Clinimetrics' Standard Operating Procedures (SOPs). The CRA is ultimately responsible for all monitoring activities, including ongoing review of the Regulatory Binder and maintenance of regulatory documentation, SAE reporting, review of source documentation, including cigarette accountability, CRF completion, query resolution, visit report and follow-up activities.

- **Initiation Visits:**
  Clinimetrics' CRA will conduct the initiation visit to include all key site personnel. There should be emphasis spent on the protocol's primary objective which is to estimate the exposure to cigarette smoke constituents who participated in the TES study. This will be done using topography devices, and collecting and analyzing both blood and urine samples. **It is imperative that the sites understand the importance of the 24 hour urine collection. It is also important that the site thoroughly understand how to collect a 24-hour urine [see protocol and investigator manual for details under Laboratory].**

- **Interim Monitoring Visits:**
  Clinimetrics' CRA will conduct two interim monitoring visits during this study. The CRA will do the first interim monitoring visit after the second subject has completed the study. If there are more than 2 subjects enrolled, the monitor will do a second interim visit. CRAs will monitor and ensure the study is progressing in accordance with the protocol and good clinical practices.

- **Closeout Visits:**
  Clinimetrics' CRA will schedule a close-out visit once all data queries have been resolved, cigarette accountability issues reconciled and the monitoring has been completed.

CRA ADMINISTRATIVE RESPONSIBILITIES

- The CRAs will be responsible for all communications with their sites. Questions they cannot address will be directed to the Clinimetrics' project manager or the Covance project manager, depending on the nature of the question. All significant communications with the site will be documented in a Standard Clinimetrics Telephone Contact Report.
- The CRAs will refer to the CRF Conventions while monitoring.
- Prior to each visit, a letter will be sent to the investigator/ study coordinator and copied to Philip Morris, confirming the planned visit. The letter will specify the tasks to be accomplished at the visit.

Trip Report Process

Clinimetrics trip report templates will be used for trip report writing. The following versions are to be used:

- Initiation TR template – version 11/22/04
- Interim TR template- version 11/19/04
- Closeout TR template- version 11/22/04

The process is as follows:

- The draft trip reports will be forwarded to the Clinimetrics' Project Manager via email within 10 working days of the visit. The PM will make comments on the cover page and forward back to CRA to be revised.
- The CRA will then forward the revised trip report (TR) and follow up letter (F/U letter) back to the PM with a copy to the PA, Alicia Mabry.
- Alicia will forward via email a copy of the TR to Mary Larson at Covance and to Philip Morris' PM, Jan Oey, B2, Hr workers
- Philip Morris will provide comments on the cover page and forward back to the Clinimetrics PM and PA within 4 days of receipt.
- Clinimetrics PA will then forward Philip Morris' comments to the CRA who will make their final revisions.
- After review and approval, the original trip report with attached confirmation and follow up letter will be sent to Central files utilizing the Clinimetrics Visit Report Transmittal Form. Central Files will forward the original report to Jan Oey at Philip Morris within 20 working days of the visit. The project manager will track timely submission of the trip reports. + ML

Trip Report Documentation

The following information must be included in the Visit Report:

- Statement describing the general purpose of the visit.
- Overall condition, organization and completeness of medical records/CRFs. Be sure to include any deficiencies or significant and/or continued completion issues.
- Document the type of source documents available for review and if they adequately support entries in the CRF.
- Summary of general study status and of any study administration problems (adequate resources, staff availability during study visits, investigator actively involved in the conduct of the study).
- Overall adherence to the protocol.
- Significant issues regarding particular subjects (SAEs, improper consent, major protocol violations, protocol exceptions granted). A section titled "Subject Specific Issues" should be included detailing major subject specific issues noted for each subject, unless it is an issue more appropriately documented in another section of the report. If there were no major subject specific issues noted for any of the subjects, this should be noted as well.
- Summary of regulatory documents review.

- Documentation of appropriate informed consent.
- Summary of all serious adverse events, notification, and need for follow-up. SAEs should be addressed on every visit report. If no SAES have occurred at a site, this should also be noted in the report.
- Status of Queries. It should be noted on every visit report if all Queries that have been sent to the site to date have been resolved. If no Queries have been sent to the site, this should be noted as well.

Study- specific documentation:

- Refer to persons enrolled into this study as "subjects" not patients.
- Do not use initials for these subjects. Only refer to the subjects by enrollment number.
- For 24 hour urine collection – document that the site is using a 1 liter cylinder to measure the 24 hour urine collection. Also, document the amount of urine volume for the 24 hour urine collection in the trip report.

When deficiencies are noted, an explanation of the action taken (or to be taken) to correct them is required.

The following sections should be included at the conclusion of the Visit Report Form:

- Subject Specific Issues.
- Previous Action Items (note those items that have been resolved by indicating 'done' in bold or a brief statement of resolution).
- Current Action Items (carry over any 'previous action items' that were not resolved).
- List of items hand carried from site.

Data Review and Collection Process Note For purposes of this study, AE =

The CRA will review and ensure the following:

- Protocol and regulatory compliance
- Each subject has signed the approved current version of the informed consent prior to study entry
- Satisfactory source documentation of subject eligibility, treatment, procedures, clinical status, and any ~~adverse events~~ (MCA to new med tx events)
- All adverse events are identified and all serious adverse events have been properly reported in a timely fashion with appropriate follow up
- All specimens are collected, stored and shipped appropriately

The CRA will perform 100% source document review. Once the CRF is monitored, the CRA will pull the white and yellow copies of the 3-part NCR CRF leaving the pink copy at the site. The CRA will complete a CRF transmittal form and submit all monitored CRFs, copies of all laboratory report results and an updated regulatory checklist to the attention of Mary Larson at Covance via pre-printed FEDEX labels that have been provided to the CRAs.

Regulatory Document Review

Regulatory document reconciliation will take place at each visit. The CRA will review the regulatory files to ensure that the files are complete and up to date. Monitoring will include

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verification of all required regulatory documentation including final protocol, CVs for the PI and sub PIs, laboratory accreditation and normal values, IRB correspondence and approvals, financial disclosure forms, study related correspondence and signed monitoring log.

- Any updates to the regulatory documents will be noted in the visit report. Also, the CRA will update the regulatory checklist during each visit and submit these updates along with the monitored CRFs that the CRA pulled during the visit. The updated checklist will (along with the CRFs) will be sent to Mary Larson at Covance via pre-printed FEDEX labels.

Serious Adverse Event Reporting

There were not SAEs reported in the first TES study, so there is no anticipation that there will be any SAEs reported in the TES Follow Up Study. However, in case there is an SAE, the CRA will document the SAE in the trip report as well as communicate their findings to the Clinimetrics' project manager as soon as they are informed. The site will be instructed to complete a MEDWATCH form and forward on to Philip Morris ~~as well as their IRB~~.

Cigarette Accountability

Cigarette accountability will be captured on page 7 of the CRF binder. There will be no other accountability log for this study. Subjects will be asked to collect the cigarette butts for a 24 hour period prior to Visit 2. The cigarette butts will be returned to the site on Visit 2. The number of cigarette butts will be counted and documented on page 7 of the subject's CRF binder. Ensure that the bar code # matches the brand of cigarettes being collected.

INFORMED CONSENT

- Verify that the version date is the latest approved version of the consent form available at the site at the time the consent was obtained.
- Verify that all required signatures (subject or legal guardian) and dates of witnesses and/or investigators/designee were obtained on the date that consent was obtained and is not dated later than the screening date.
- Verify that all pages of the consent are present and that all required 'fill-in' fields have been completed.
- Verify that documentation is present in the source that the informed consent was obtained prior to the implementation of any protocol specific procedures.
- Verify that the original informed consent form is filed in the subject source record or is in the regulatory binder at the investigational site. A copy of the consent form should be provided to the subject or guardian.
- Any errors in the informed consent procedure must be explained in a memo to file that is to be placed with the consent.

PROTOCOL SPECIFIC GUIDELINES

CRF Review

Source Document Review

100% Source document review will be performed for all subject enrolled into the study

- Ensure that visit dates on the CRF correspond with the dates of the source documents.
- Ensure that source documents are available and adequately support the data in the CRFs.
- Source Documents created by Covance must be used as source documentation for this study.

General CRF Completion Guidelines

- All CRAs and study coordinators have been provided with a copy of the CRF completion instructions.
- All CRFs will be printed on 3-part NCR paper. The white/yellow copies will be pulled and sent to Covance. The pink (bottom) copy will remain at the site.
- Review the CRF for completeness, legibility, accuracy, consistency and that it follows protocol requirements. All entries should be in black ink.
- Ensure that the writing on the CRF appears clearly on the NCR copy.
- Check for transcription errors.
- Discrepancies between the CRFs and the source documents should be noted and corrected by the site personnel before the CRF leaves the site. Errors should be lined out with a single line, the correction inserted and the correction initialed and dated. Since the source document should be the first place that data is recorded, it is suspicious when the CRF entry differs from the source, and the site says the CRF is correct. In some cases, the site may have been transcribing data from a clinic chart to a research source document (although this is not necessary), and an error was made. If there is an explanation to an error in the source document, a correction to the source can be made with a note to explain the error.
- Dates should be entered as indicated on the form, for example, dd/mmm/yyyy (day/month/year). A partial or estimated date is preferable to an incomplete one (i.e unk-JUN-2004, --JUN2004) or even a year (i.e 2004, ---2004, unk-unk-2004).
- After the CRFs are sent to Covance, ~~any corrections to the data will be documented on the CRF~~. Discrepancies requiring action by the investigative sites will be raised as queries on a DCF (Data Correction Form) page on query.
- Mary – not sure if all of this is true (I guessed) Queries will be issued to the sites on an ongoing basis. The reports will ~~contain one query per page, and will contain~~ areas for the site's response, signature, and date. A copy of the report will remain at the site for their records, and the resolved query with site signature will be returned to Covance.

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Specific CRF Completion Guidelines

Inclusion/Exclusion Criteria –Page 1

1. "Yes" or "N/A" must be checked for all inclusion criteria in order for the subject to be eligible for the study.
2. "No" must be checked for all exclusion criteria in order for the subject to be eligible for the study.

Subject Eligibility- Page 2

1. Date of Informed Consent – Mary – which date should this be?
2. Inclusion Criteria- Answer must be yes
3. Exclusion Criteria – Answer must be no
4. Exemption – Answer is N/A

Medical History – Page 3 (new nurse wants)

1. This page captures all "AEs" for the subject.
2. Each line should have only finding.

Height/Weight – Vital Signs – Urine Pregnancy Test- Page 5

1. Ensure all measurements are transcribed appropriately from source.
2. All women must have pregnancy test done.

Blood Sampling-24 Hour Urine Collection –UPC code- Page 6

1. Blood sampling- Ensure that the "collection date" matches CCLS lab requisition.
2. 24 – Hour Urine- Ensure that the total volume is 750ml. Subject can not continue on the study unless volume of urine is equal to or greater than 750ml.
3. UPC code – Verify the UPC code against the copy of the pack of cigarettes that the subject brings into the clinic.

(ensure all data correct)

Topography –Page 7

1. Ensure that the serial number of the device matches the number on the material transfer form.

Concomitant Medications –Page 8

1. Ensure that all conmeds that the subject is taking for the last 30 days prior to Visit 1 are documented on this page.
2. Use trade names for combination drugs and generic names for single meds.
3. Ensure that the onset date of the conmed is not prior to the respective medical history onset date.

Smoking History – Page 9 and 10

1. These 2 CRFs are also source documents. It is important that someone reviews these 2 pages for completion prior to allowing the subject to leave the clinic. Emphasize that no questions should remain blank on these 2 pages.

+ follow ship cards.

Study Completion

1. Date of Study Completion is the same date as Visit 2.