LUCERNO DYNAMICS, LLC

A Study to Assess the Impact of Moderate/Significant Infiltrations on the Standardized Uptake Values of Target Lesions

Protocol Number:	LUC-2017-001
Version:	0
Device:	Lucerno Dynamics Lara™ System for QA/QC in Imaging
Sponsor:	Lucerno Dynamics, LLC 142 Towerview Court Cary NC 27513
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Approval:

Study Principal Investigator Signature (Name and Title)	*Date*
Study Co-Principal Investigator Signature (Name and Title)	*Date*

This confidential information about a medical device product is provided for the exclusive use of Study PIs of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Study Principal Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Lucerno Dynamics with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: LUC-2017-001

Protocol Title: A Study to Assess the Impact of Moderate/Significant Infiltrations on the Standardized Uptake Values of Target Lesions

Protocol Date: December 19, 2017

_____ _____

Study Principal Investigator Signature *Date*

_____

Print Name and Title

_____ _____

Study Co-Principal Investigator Signature *Date*

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LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CT	Computed Tomography
FDA	Food and Drug Administration
FDG	^{18}F-Fluorodeoxyglucose
FOV	Field of View
GCP	Good Clinical Practice
IRB	Institutional Review Board
MTV	Metabolic Tumor Volume
NM	Nuclear Medicine
PET	Positron Emission Tomography
QA	Quality Assurance
QC	Quality Control
Study PIs	Study Principal Investigators
TLG	Total Lesion Glycolysis
VOI	Volume of Interest
ROI	Region of Interest
WB	Whole Body
SUV	Standardized Uptake Value

PROTOCOL SYNOPSIS

TITLE	A Study to Assess the Impact of Moderate/Significant Infiltrations on the Standardized Uptake Values of Target Lesions
SPONSOR	Lucerno Dynamics, LLC
NUMBER OF SITES	1
RATIONALE	A widely used semi-quantitative parameter to assess tumor status is the standardized uptake value (SUV). SUV estimation accuracy can be impacted by many variables. Today there still exists a significant amount of variability in PET/CT results in test and re-test studies. This variability can be introduced by instrumentation and subject-specific factors. Variability reduces image quality and increases the required changes in tumor quantification to reflect real tumor response or progression. PET/CT scanning process requires that the entire net injected dose of radiolabeled tracer is administered intravenously as a bolus. The quality and quantification of a PET/CT image is highly dependent on the uptake of radiolabeled tracer. Boellaard et al. have indicated infiltrations could potentially underestimate SUV measurements by as much as 50%. Infiltrations and obstructions are not uncommon.
STUDY DESIGN	This is a prospective single-center study with no therapeutic intent.
PRIMARY OBJECTIVE	To characterize impact of moderate or greater infiltrations on standardized uptake values.
EXPLORATORY OBJECTIVES	To estimate the impact that infiltrations may have on initial assessment and/or response assessment in accordance with PERCIST criteria. To estimate the effect of moderate or greater infiltrations on metabolic tumor volume and total lesion glycolysis.

NUMBER OF SUBJECTS	The number of subjects will be determined based on the number of moderate or greater infiltrations at the site.
SUBJECT SELECTION CRITERIA	**Inclusion Criteria**: Subjects with solid tumors or lymphoma undergoing PET/CT scan who have at least one measurable target lesion and sustain a moderate or greater infiltration. **Exclusion Criteria:** Subjects unwilling or unable to tolerate a repeat PET/CT scan. Subjects with meaningful medical intervention between PET/CT scans that would likely impact SUV. Subjects with follow up moderate or severe injection infiltrations that would likely impact the SUV. Patients for whom an infiltration score cannot be determined, such as when ports or other central lines are used. Pregnant patients. Subjects who are not able to read/understand English.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Patients who experience a moderate or greater infiltration will be invited for a repeat PET/CT scan. Subject participation in this study is limited only to the few minutes they are questioned after their first scan and before their repeat scan, and for the time it will take for the repeat scan. These questions are designed to try and ensure both scans were conducted under similar subject conditions (fasting levels, prior activity levels, etc.) The questions should not require more than 15 minutes total. Final data analysis will be completed within 3 months of enrolment of the final subject.
STATISTICS **Primary Analysis Plan**	Analyses will be descriptive in nature because the sample size of the group who will return for re-testing is challenging to forecast a priori. We anticipate enrolling up to 20 patients in 12 months based on the infiltration rate at WFB and accounting for ongoing quality improvement efforts.
Rationale for Number of Subjects	All subjects undergoing PET/CT who experience a moderate or greater infiltration will be invited back for a repeat scan.

1.0 INTRODUCTION AND BACKGROUND

PET/CT scanning is becoming progressively more important to the management of patients with cancer due to its accuracy and convenience in presenting anatomical and functional information. Oncology PET/CT scans are often used to stage cancer and assess therapy response. Quantification of PET/CT results is increasingly being used. A widely used semi-quantitative parameter to assess tumor status is the standardized uptake value (SUV). SUV estimation accuracy can be impacted by many variables. Therefore, producing high quality PET/CT images requires rigorous protocols of image acquisition and analysis.

Today, there still exists a significant amount of variability in PET/CT results in test and re-test studies [1]. This variability can be introduced by instrumentation and patient-specific factors. Variability reduces image quality and increases the required changes in tumor quantification to reflect real tumor response or progression. Weber's recent multi-center study of NSCLC found a 30% SUV decrease (in defining therapeutic response) or a 40% SUV increase (in defining progression) is required to have confidence that the results are indicative of metabolic response or metabolic progression, rather than a reflection of variability in the measurement of the PET/CT process [2].

Accurate SUV calculation requires that the entire net injected dose of radiolabeled tracer is administered intravenously as a bolus. The quality and quantification of a PET/CT image is highly dependent on the uptake of radiolabeled tracer. Boellaard et al. have indicated infiltrations could potentially underestimate SUV measurements by as much as 50% [3]. Infiltrations and obstructions are not uncommon. Single center studies have demonstrated that improper injections of radiolabeled tracer for PET can occur in 10 - 21% of cases [4, 5, 6].

Recent studies using a novel QA/QC tool (Lara^{TM} System) for the radiotracer injection process revealed that current means to detect infiltration do not completely identify all infiltrations/obstructions [7]. Since infiltrations may not be visible in the standard field of view (FOV) and since the impact of a peripheral circulatory obstruction may not be visible even if an injection site is in the FOV, it is possible for reading and treating physicians to be unaware that a patient's image and quantification has been impacted. Additionally, when current means do detect an infiltration, they under-represent the severity because they are not capturing that infiltrations often resolve during the uptake period. As a result, infiltrations or obstructions may cause SUV inaccuracy and could adversely impact staging and tumor assessments.

The FDA-listed Lucerno Dynamics Lara^{TM} System is comprised of sensors, a reader and software. The sensors are connected to a reader that provides temporary data storage. By using similar principles as PET scanning technology (i.e., scintillating crystal and photomultiplier), the sensors measure the presence of radiolabeled tracer in target areas of interest. The system software that has been developed uses time activity curves (TACs) to provide a way to determine whether radiolabeled tracers commonly used in PET/CT remain pooled near the injection site during the uptake period, rather

than circulating in the vascular system. Past and ongoing studies using standard PET/CT and dynamic images have confirmed the Lara™ System is a better tool than current imaging to identify and characterize the presence of radiotracer near the injection site during uptake. Because the Lara™ sensor is located near the injection site, it captures all infiltrations and obstructions and is agnostic to imaging FOV. With a one second frame rate, Lara™ dynamically captures radiotracer presence during the entire uptake period, and therefore better characterizes infiltrations as compared to static images taken at 60 minutes post injection. Lara's TAC feedback on the fidelity of an FDG injection of the entire uptake period could help reduce erroneous infiltration interpretations.

Because Lara will be able to better identify and characterize moderate or greater infiltrations, Lucerno will assist the clinical site in the design and execution of a study to assess impacts of these infiltrations. All medical management of subjects participating in this research is at the discretion of the site medical care team and is not part of the research protocol.

2.0 PURPOSE OF THE STUDY

A widely-used parameter to quantify uptake of radiolabeled tracer is the standardized uptake value (SUV), calculated by normalizing radiolabeled tracer activity concentration in a volume of interest (VOI) to the decay-corrected injected activity and body mass. SUVs allow semi-quantitative evaluation of disease and therapy response. Accuracy of SUV estimation assumes the entire net injected dose is administered intravenously as a bolus injection. Improper injections have been shown in previous studies to impact SUV measurements [3, 4]. In the few published studies measuring infiltration rates in PET, radiolabeled tracer infiltration occurs in 10–21% of clinical exams [4, 5, 6]. Phase 1 of an ongoing quality improvement project at Wake Forest Baptist Health using the Lara™ device has shown an infiltration rate of 13.3%. Additionally, infiltrations may impact a reading physician's ability to properly stage a patient's cancer, since metastatic lesions may not be visible in infiltrated cases.

The purpose of this study will be to characterize the impact of moderate or greater infiltrations on standardized uptake values.

2.1 Objectives of the study

2.1.1 Primary Objective

To characterize impact of moderate or greater infiltrations on standardized uptake values of solid tumors or lymphoma.

2.1.2 Exploratory Objectives

- To estimate the impact that infiltrations may have on initial assessment and/or response assessment in accordance with PERCIST criteria.
- To estimate the effect of moderate or greater infiltrations on metabolic tumor volume and total lesion glycolysis.

2.2. Anticipated duration of the study

Participation in the study is limited to the time from the baseline PET/CT to the repeat PET/CT scan which is anticipated to be no more than one week. While subjects will only answer questions for a total of less than 15 minutes to try and ensure the conditions for each PET/CT scan are standardized as much as possible, these two sessions of questions may be 1 to 7 days apart. Patient accrual will be closed after 12 months.

3.0 PROTOCOL

3.1 Protocol number and title

LUC-2017-001 A Study to Assess the Impact of Moderate/Significant Infiltrations on the Standardized Uptake Values of Target Lesions

3.2 Protocol version number and date

Version 0, December 19, 2017

3.3 Project design

This is a prospective, single-center, study with no therapeutic intent.

3.4 Subject selection

3.4.1 Inclusion criteria

Subjects with solid tumors or lymphoma undergoing F-18 FDG PET/CT scan who have at least one measurable target lesion and sustain a moderate or greater infiltration.

3.4.2 Exclusion criteria

- Subjects unwilling or unable to tolerate a repeat PET/CT scan.
- Subjects with meaningful medical intervention between PET/CT scans that would likely impact SUV.
- Subjects with follow-up moderate or greater infiltrations as determined by the PI and Lara score.
- Patients for whom an infiltration score cannot be determined, such as when ports or other central lines are used.

- Pregnant women.
- Subjects who are not able to read/understand English

3.4.3 Anticipated number of subjects

All subjects who experience a moderate or severe infiltration will be invited back for a repeat scan. Based on historical data, Wake Forest Baptist quality improvement initiatives have been implemented to reduce the number of infiltrations. We would therefore estimate up to 20 subjects in the next twelve months. Data will also be captured on the CRF for any patients who return for additional follow-up scans (after completing the test/re-test portion of the study).

3.5 Study procedure

The Lara™ System is currently commercially available and is being used on site as part of a Quality Improvement project on all patients undergoing PET/CT studies. The Lara™ System will continue to be used on all patients undergoing PET/CT scans at the completion of the Quality Improvement Study to provide ongoing quality control and quality assurance of the injection process. Patients whose scans are determined by the Nuclear Medicine physician, or their designee, to have a moderate or greater infiltration based on review of the standard PET images and/or Lara™ TACs will be asked to return for a repeat PET/CT scan within 1-7 calendar days. In the event that the follow up scan shows any infiltration; the Nuclear Medicine physician or designee will be consulted to determine appropriate next steps. Site will duplicate the PET/CT protocol of the initial scan as carefully as possible for the follow up scan. Factors that will help ensure consistency of scan conditions to be recorded on the Case Report Form (CRF) (Appendix 1) include (but are not limited to):

- Same pre-procedure process and instructions to subject
- Time of day
- Glucose
- Time from injection to scanning
- PET/CT bed protocol
- Fasting and pre-scan activity level
- Subject weight
- BMI
- Prescribed FDG dose
- Flush volume
- Concomitant medications
- Any other data deemed pertinent by the technologist and/or Nuclear Medicine physician

3.5.1 Withdrawal of subjects due to non-compliance

Non-compliance will only occur if a subject does not follow the same pre-PET/CT scan guidance that they followed for their initial scan. In the event of reported non-compliance by a subject, the Nuclear Medicine physician will be consulted on appropriate action to take.

3.5.2 Procedures to assess efficacy

The study does not involve evaluation of efficacy.

3.5.3 Procedures to assess safety

The study does not involve evaluation of safety.

3.5.4 Schedule of study visits

Patients who are determined to have a moderate or greater infiltration on their routinely ordered PET scan will be invited back for a repeat scan within 7 days of the initial scan.

3.6 Study Objectives

3.6.1 Primary Objective

To measure the impact of moderate (or greater) infiltrations on standardized uptake values.

3.6.2 Exploratory Objectives

- To estimate the impact that infiltrations may have on initial assessment and/or response criteria assessment in accordance with PERCIST criteria.
- To measure the impact of moderate or greater infiltrations on metabolic tumor volume and total lesion glycolysis.

3.6.3 Sample size determination

The sample size of the group who will return for re-testing is challenging to forecast a priori due to ongoing quality improvement efforts to reduce infiltrations The study will enroll patients for up to 12 months, or will be terminated at 20 patients if reached in less than 12 months.

3.6.4 Data Analysis

Upon the determination of an infiltrated subject, the technical staff will notify the Nuclear Medicine physician to determine the severity and appropriateness of the subject for the study. To qualify for the study, the subject will need:

- at least one target lesion; and

- at least a moderate infiltration as determined by visual analysis and/or infiltration score from the Lucerno Dynamics' Lara™ system software

Data will be analyzed on each individual subject after the second imaging session. The scans will be presented in tandem such that simultaneous measurements may be performed using a qualified image analysis program, such as MIM version 6.5. Up to five target lesions will be assessed, chosen to include the target lesion or lesions defined under the PERCIST criteria [8]. For each lesion, SUV peak will be measured, and a volume contour will be created using mean liver SUV+2SD as a threshold., SUVmean, metabolic tumor volume, and total lesion glycolysis will be measured from the contour. The lesions chosen will be the same for each scan, however differences in the scans may affect the volume contour. Liver and blood pool measurements will also be made as for PERCIST criteria.

SUV will be descriptively compared for the original and re-test. Our expectation is that SUV will increase at the re-test, although we are not amply powered to conduct a rigorous statistical test. We will also evaluate the relationship between SUV values and the Lara score by computing a Pearson's correlation coefficient. We hypothesize this correlation will be positive.

We hypothesize that presence of venous stasis (a cessation or impairment of venous flow) may have an influence on the relationship on SUV scores. We will conduct a sensitivity analysis by conducting analyses with and without stasis cases. Specifically, we will compare the % change in SUV values between test and re-test and the correlation coefficient of % SUV change and Lara score in the samples including and excluding stasis cases.

To assess the exploratory objective of whether extravasation of radiotracer could influence initial staging, for patients where the type of primary solid tumor is known the T, N, and M stages will be assessed to the extent possible by PET/CT for each scan and an overall stage assigned. This will be done even if the scan was performed for response assessment or follow up. No additional imaging or clinical information will be used and it is recognized that this assessment may not generate the true clinical stage. However, the comparison between the two scans will still provide information regarding the risk of changing stage based on missed or mischaracterized lesions after an extravasation event. To provide more granular information, the number of FDG avid regional nodes and number of FDG avid non-nodal metastases (capped at 25 each) will also be recorded for each scan.

For the exploratory objective of whether extravasation can influence apparent response to therapy, we will use the infiltrated and repeat scans to explore the impact of infiltrations on PERCIST criteria if there is an existing PET/CT scan for

comparison. This other PET/CT scan could either be a prior or a follow-on PET/CT scan that has a Lara-validated injection.

All scans will be analyzed by a qualified Nuclear Medicine physician and reported using the study imaging charter. Any measurements made for the clinical reports will not be used for this analysis. To mitigate bias, a second blinded radiologist will independently analyze the scans.

4.0 RISK ANALYSIS

Minimal risk to the patient arises from exposure to radiation from one additional PET/CT. There are no anticipated risks associated with the effort to help assure both PET/CT scans protocols are as similar as possible. It is possible that the repeat scan will reveal additional abnormalities not seen on the initial scan, which could cause psychological distress. There is a theoretical risk of disclosure of protected health information. To minimize this risk, all data collection will be performed in the Nuclear Medicine department. Limited PHI will be included in the research record, and all data will be stored on encrypted devices per heath center policy. A log of study accession numbers, which could reidentify patients through the electronic medical record, coupled to study patient identifier will be maintained on an encrypted device to allow auditing of the data. The study team will comply with all site procedures and policies to protect confidentiality and minimize any risk to subject privacy.

4.1 Adverse event reporting

Serious Adverse Events will be reported and recorded with the patient data on the Adverse Event Form. Any serious adverse event, including loss of confidentiality, will be reported to the IRB per site requirements, and to the study sponsor within 24 hours of knowledge of the event. There are no experimental drugs or devices being used in this study.

4.2 Withdrawal of subjects

Any subject in the study may withdraw from the study at any time. In such cases the reason for withdrawal will be recorded and determination will be made by the site PIs as to its association with the research.

5.0 MONITORING PROCEDURES

Monitoring of the study for compliance with the clinical protocol and with FDA regulations will include at least one on-site visit by clinical staff of Lucerno. The Study PIs will permit direct access of the study monitor and appropriate regulatory authorities to the study data and any corresponding source documents to verify the accuracy of the data.

6.0 INFORMED CONSENT

Subject consent will be obtained for all subjects willing to participate in the clinical study. No study procedures (data collection) may be done until the subject has provided a signed informed consent. The consent form will contain non-technical language describing the study procedures.

Once a potential subject has been identified for study participation (a moderate or greater infiltration has been noted), the Investigator or authorized designee will approach the subject to explain the purpose and scope of the clinical study, along with prospective risks, and benefits of participation. The subject must be given the opportunity to ask questions about the study and must be given sufficient time to decide to participate in the study or not. Any additional information requested by the prospective subject should be provided.

If the subject agrees to participate, the informed consent form must be signed and personally dated by the subject. The investigator or an authorized member of the research team who has witnessed the subject's signature must also sign and date the informed consent, prior to enrollment of the subject. A copy of the completed informed consent form must be provided to the subject. Local IRB regulations regarding obtaining informed consent must be followed. The subject's medical record should have a notation regarding the signing of the informed consent.

If a subject is unable to provide written consent due to limitations in ability to read or write, informed consent shall be obtained with the subject's LAR (legally authorized representative) and an independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the subject and, whenever possible, the subject shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

The consent form will include patient authorization to release PHI limited to that collected in the study to Lucerno Dynamics.

7.0 IRB INFORMATION

The protocol will be reviewed and approved by the site IRB prior to study initiation. Adverse events will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol will be in the possession of the Study PIs before the study is initiated. The IRB's unconditional approval statement will be transmitted by the Study PIs to Lucerno prior to study initiation. This

approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

8.0 ADDITIONAL RECORDS AND REPORTS

8.1 Data handling and record-keeping

Data will be captured using the Lara™ System, the site PET/CT scanner and a study CRF. Other than the scintillation data captured, the following information is also captured via drop down menus on the home screen at the time of data download:

Subject Height - in or cm

Subject Mass – lb. or kg

Subject Age Group: <16, 16-49, 50-69, >70

Subject Glucose:

Radiotracer:

Dose (mCi):

NM Technologist performing the injection

Flush Volume:
Injection Orientation – Unknown, Right, Left

Injection Locations – Unknown, Antecubital, Forearm, Hand, Wrist, Foot, Port, Other

Injection Technique – Unknown, Butterfly, IV, IV Drip, Straight Stick, Other

Auto Injection – Unknown, No, Yes

Needle Gauge – Unknown, 14, 16, 18, 20, 22, 23, 24, 25

At the time of data entry, the NM Technologist enters the subject's identifying hospital record number. This number is cross-referenced to a Lucerno identification number to allow the site to identify the subject and match the data with the subject. The cross reference between the hospital and Sponsor numbers is recorded at the site. Only Lucerno's identification number is transmitted, with other collected data, to the Lucerno server. The transmission is encrypted and contains no Protected Health Information.

Completed case report forms will be scanned and sent via secure e-mail to Lucerno Dynamics on a pre-determined schedule. All study documents, including paper case report forms will be kept in a secured, locked location at Wake Forest Baptist Medical Center.

8.2 Record maintenance and retention

Lucerno and the Study PIs will maintain records to include:

- IRB correspondence (including approval notifications) related to the clinical protocol including copies of adverse event reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and any protocol amendments
- Signed Study PIs Agreements and Certifications of Financial Interests of Clinical Investigators
- Curriculum vitae (Study PIs and any clinical protocol sub-investigators)
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for the Study PIs and key staff
- Source Documents or certified copies of Source Documents
- Monitoring visit reports
- Copies of study correspondence including any notifications of adverse effect information
- Subject screening and enrollment logs
- Subject Case Report Forms
- Signed Subject Informed Consent Forms
- Subject identification code list
- Final report

Lucerno and Study PIs will retain the specified records and reports for at least two years following completion of the study. No records will be destroyed without explicit permission from Lucerno Dynamics.

9.0 STUDY RESULTS AND PUBLICATION

9.1 Ownership of Study Results

Site and Lucerno shall jointly own all study data, reports and the results of the study ("study results") as described in the SUV Study Agreement.

9.2 Communication of Study Results

Lucerno will abide by all applicable laws regarding communication of safety information and study results as described in the SUV Study Agreement.

10.0 PUBLICATIONS AND PRESENTATIONS

The Study PIs shall register the study on any appropriate public registries, such as clinicaltrials.gov, as required by applicable law or regulation. Publication of the study results will be a joint responsibility between Lucerno and the Study PIs.

References

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5. Osman MM, Muzaffar R, Altinyay ME, Teymouri C. FDG dose extravasations in PET/CT: frequency and impact on SUV measurements. Front Oncol. 2011;1:41. doi:10.3389/fonc.2011.00041.
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8. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009;50(Suppl 1):122S–150S.

APPENDIX I

Case Report Form