

RESEARCH RESOURCES.

FACTS:

DEPARTMENT OF CLINICAL RESEARCH

The OHRP/NIH definition of research is any systematic investigation designed to develop or contribute to generalizable knowledge.

IRB

All human research studies are reviewed by the

FORMS

IRB before they begin and at least once annually to evaluate risks to subjects and compliance with

INVESTIGATOR'S GUIDE

federal regulations and institutional policies.

GLOSSARY

IRB administrators are available to assist researchers with application submissions.

MCDH EDUCATION PACKET & TEST

fax: (972)-566-4715, mail or bring answer sheet to the Clinical Research Department (12200 Park Central Dr., 1-Forest Ste. 500, Dallas, TX 75251)

DEPARTMENT OF CLINICAL RESEARCH

AT A GLANCE

The MCDH Department of Clinical Research is staffed by a professional team of research scientists, engineers, administrative specialists and research nurses. The expertise of the staff covers a wide range of disciplines including: biostatistics, cardiopulmonary physiology, life sciences, medical biophysics, nursing and research administration.

MISSION

To provide complete research support services to all individuals interested in developing research projects which will lead to improvements in the prevention, diagnosis, and treatment of diseases.

SERVICES

Assistance with research development and project design; completion of research committee requirements (e.g., IRB); research grant preparation and management; biostatistics and data management (e.g., data base development, data analysis); and biomaterials and product testing.

To provide these services, the Department's resources and program capabilities include biomaterials testing laboratory, clinical new pharmaceutical/device human clinical studies (IND/IDE) expertise, computer facilities, desktop publishing/graphics.

DCR PERSONNEL

Joseph Zerwekh, PhD, Director of Clinical Research (x6953) (Research Contract/Grant Preparation & Management)

joseph.zerwekh@hcahealthcare.com

C. Yvette King, BS, CCRP, CIM, IRB Supervisor (x6060) (IRB Requirements &/or Submissions)

christelle.king@hcahealthcare.com

Morley Herbert, PhD, Biomedical Research & Biostatistician (x6716)

morley.herbert@hcahealthcare.com

Nancy Nardelli, RN, CCRC, Nursing Research Coordinator (x4350)

nancy.nardelli@hcahealthcare.com

IRB (Institutional Review Board)

An Institutional Review Board has been established (45 CFR 46; 21 CFR 56) to review the scientific merit, medical necessity, educational value, and moral, ethical, legal and fiscal aspects of all clinical research at Medical City Dallas Hospital (MCD). All research studies are reviewed by the IRB before they begin & at least once annually to evaluate the risks to subjects and compliance with federal regulations and institutional policies.

The mission of the IRB is to ensure that research is conducted ethically, in compliance with federal regulations and institutional policies, and that the rights and welfare of human subjects in the research are protected.

The MCDH North Texas Institutional Review Board is registered with the **Office for Human Research Protection (IRB00000852)** and its **Federal-Wide Assurance number is FWA00000220**. This agreement is between MCDH North Texas IRB & DHHS stating that MCDH North Texas IRB is guided by the ethical principles of the Belmont Report & will comply with federal regulations for all research involving human subjects. Agreements are in place to have the MCDH IRB serve as the central IRB responsible for research projects at Denton Regional Medical Center, Las Colinas Medical Center, Lewisville Medical Center, Medical Center of Arlington, Medical Center of McKinney, Medical City Dallas Ambulatory Surgery Center and Green Oaks Hospital.

FEDERAL REGULATIONS

All research involving human subjects, regardless of funding source, conducted at or in affiliation with MCD shall be conducted in accordance with federal regulations.

Applicable federal regulations include, but are not limited to:

- 45 CFR 46, generally known as the Common Rule & subparts B, C & D
- 21 CFR 50 & 56, Human Subject Protection (Informed Consent) & IRBs
- 21 CFR 312, Investigational New Drug Application
- 21 CFR 812, Investigational Device Exemptions

AUTHORITY OF THE IRB

The IRB has the authority to approve, require modifications of, or disapprove all human research that falls within its jurisdiction. The IRB monitors & conducts continuing review of approved research at intervals of at least once per year. The IRB has the authority to observe or have a third party observe the consent process. The IRB takes actions to comply with federal regulations or other applicable laws, including action to suspend or terminate approval of research. The IRB must report to appropriate MCDH institutional & federal government officials & any funding agency: any suspension or termination of research, any unanticipated problems involving risks to subjects & any serious or continuing noncompliance with IRB requirements.

IRB FEES

All industry-sponsored applications submitted to the IRB for initial review will be assessed a fee for new applications in the amount of \$1500 for full board review. The fee for continuing review of such studies is \$500. There is no fee for amendments to protocols. Applications supported by State, Federal, non-profit foundation, or internal funds are excluded from these charges.

NORTH TEXAS IRB CONTACT INFORMATION

Yvette King, BS, CCRP, CIM
IRB Supervisor
(x6060)

Allan Naarden, MD
IRB Chairman
(x4718)

FORMS

NORTH TEXAS INSTITUTIONAL REVIEW BOARD AT MEDICAL CITY RESEARCH PROGRESS REPORT

(This form **MUST** be completed in its entirety even if & although enrollment is closed & waiting to publish or submission for publication is pending)

Protocol Number and Title: _____

Principal Investigator: _____

Reporting Period: _____

- 1) Subject Experience
 - a) Number of subjects entered this period _____ Total number entered _____
 - b) Number of subjects continuing in treatment or follow-up _____
 - c) Number of subject withdrawals _____
 - d) Do you plan to continue enrolling new subjects? YES NO
 - e) When do you expect the study to be completed? _____
 - f) Do you wish to close this study? YES NO
- 2) Have any **unanticipated risks** been discovered since the last IRB review? YES NO
If yes, please describe (use additional sheets as necessary).
- 3) Have there been any **significant new findings** which may relate to the subjects' willingness to continue participation? YES NO If yes, please describe (use additional sheets as necessary).
- 4) Have there been any **adverse events** with any patients in this study? YES NO
If yes, were these reported to the IRB? YES NO If not, please explain why not & provide descriptions of the adverse event (use additional sheets as necessary)
- 5) Are you having any **problems** with this study? YES NO If yes, please explain (use additional sheets as necessary).
- 6) Have any **changes** been made to the study since it was approved? YES NO
If yes, have those changes been approved by the IRB? YES NO If not, please explain in detail the changes and why they were not submitted (use additional sheets as necessary).
- 7) Have you submitted/presented any **abstracts, publications or presentations**? YES NO
IN PUBLICATION If yes, please provide a copy of all abstracts, publications and/or presentations (use additional sheets as necessary).

Principal Investigator/Coordinator Signature

Date

RETURN TO: Department of Clinical Research, Medical City Dallas Hospital, 12200 Park Central Dr., 1-Forest Ste. 500, Dallas, TX 75230 (972/566-6060 ph & 972/566-4715 fax)

(HIPAA Authorization)

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

You have a right to privacy. This means all information obtained as a part of this study will only be used as described below. The results of this study may be published in a scientific book or journal. If this is done, your name will not be used without your specific written permission. In addition, if photographs, audiotapes or videotapes are taken during the study, then you must give special written permission for their use. All information about you from this research project will be kept in a locked space.

By signing this Agreement you agree to allow (*put name of investigator here*) and his/her staff (**Researchers**) and the study sponsor, (*put name of sponsor here*) (**Sponsor**), to use and disclose health information that identifies you for the purposes described below. You also agree to permit Medical City Dallas Hospital, its staff, your doctors, and your other health care providers to disclose health information in your medical records to the Researchers and Sponsor for the purposes described below.

The Researchers and the Sponsor may use and share your health information to conduct the research. They may use your health information as described in the informed consent. They may disclose your health information as required by law and to representatives of government organizations, review boards, and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research.

If information that could be used to identify you has been removed, then the information that remains is no longer subject to this Authorization and may be used and disclosed by the Researchers and Sponsor as permitted by law. Once your health information has been disclosed to another party as indicated above, federal privacy laws may no longer protect it from further disclosure. However, the Researchers and Sponsor agree to protect your health information by using and disclosing it only as permitted by you in this Authorization. These limitations will continue even if you revoke (take back) your Authorization.

You do not have to give this permission and it is all right to refuse to sign this section of the consent form. Your doctor will still treat you even if you do not give your permission for this release of information. Your insurance will still pay your medical bills if you do not give your permission. However, since it is important for the people listed above to have access to your information, if you do not sign this Agreement, you cannot be in the research study.

While the research is in progress, you will not be allowed to see any health information that is created or collected. After the research is finished, you may see the information if you wish. Unless permission is specifically withdrawn, this permission will NOT expire at the end of the research study.

You will be given a copy of this Authorization after you have signed it.

Signature of Patient

Date

Printed Name of Patient

North Texas Institutional Review Board at Medical City

7777 Forest Lane, 1-Forest Ste. 500 Dallas, TX 75230 972/566-6060 Phone 972/566-4715 Fax

REQUEST FOR WAIVER OF HIPAA PRIVACY AUTHORIZATION FOR RESEARCH

IRB PROTOCOL NUMBER: _____

STUDY TITLE: _____

PRINCIPAL INVESTIGATOR: _____

ADDRESS: _____

PHONE NUMBER: _____

WAIVER REQUEST:

1. I am requesting this waiver of authorization for the following purpose (select only one of the following two items):

___ The collection of initial screening data to recruit potential research subjects, or to determine study eligibility only.

___ Retrospective reviews, research database or repository, or other research study where obtaining a signed authorization is not practical.

REQUEST FOR HIPAA WAIVER (Cont.)

2. The following protected health information will be created, collected, used and/or disclosed for the purpose of conducting this research (list the specific protected health information here):

3. I certify that the use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals based on at least the following elements (select applicable items):

- a. An adequate plan is in place to protect the identifiers from improper use and disclosure. The plan is as follows (select all that apply):

All electronic study will be password protected.

Passwords will be changed on a regular basis.

Access to study data will be restricted to authorized study personnel only.

All paper study records will be kept in locked file cabinets and access limited to authorized study personnel only.

Other _____

b. An adequate plan is in place to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law. The plan is as follows: _____

c. The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by HIPAA regulations.

REQUEST FOR HIPAA WAIVER (Cont.)

- 4. I certify that the research could not practicably be conducted without this requested waiver.
- 5. I certify that this research could not practicably be conducted without access to and use of the protected health information.
- 6. I certify that I will only access the minimum amount of PHI necessary to accomplish the purpose(s) of the research described under this waiver.

I attest that the above statements are correct and complete to the best of my knowledge.

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

FOR IRB OFFICE USE ONLY

This waiver was approved under: Full Review_____ Expedited
Review_____

Signature of IRB chair or IRB Administrative Representative

Approval Date

INVESTIGATOR'S GUIDE

North Texas Institutional Review Board at Medical City

12200 Park Central Dr.,
1-Forest Ste. 500
Dallas, TX 75251
972/566-6060 Phone
972/566-4715 Fax

January 3, 2011

Dear Physicians/Study Coordinators:

Attached please find information which will aid you in submitting a new study to the IRB. The enclosed instructions and model forms should help guide you through each requirement.

Please note the **EDUCATION REQUIREMENT** for Protection of Human Research Subjects. This training must be done & renewed every two years by investigators/co-PIs/coordinators & annually for IRB members (<http://phrp.nihtraining.com>, the MCDH Protection from Research Risks educational program {which can be obtained from the Clinical Research Department or www.citiprogram.org select "Biomedical Course Only"}) & provide a copy of the certificate of completion to our office. All investigators must disclose information regarding financial compensation by an outside source and health information release requirements.

If you have any questions, please call Yvette King at (972) 566-6060.

Sincerely,

Christelle Yvette King, BS, CCRP, CIM
Supervisor Institutional Review Board,
Department of Clinical Research

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Attachment

Institutional Review Board

Table of Contents

Submission Requirements for New Protocol Review.....	3
Model Cover Letter.....	4
Protocol Summary Outline.....	5
Basic Elements of Informed Consent.....	6
Model Informed Consent.....	8
Assent by Minors (7 - 17 years of age).....	12
Assent to Participate in Research (7 - 12 yrs. of age).....	13
Assent to Participate in Research (13 - 17 yrs. of age).....	15
Parent's Waiver of Child's Consent (7 - 17 yrs. of age).....	17
Additional Elements of Consent Needed for Genetic Studies.....	18
HIPPA Health Information Disclosure Form.....	19
After Approval Requirements.....	20
Meeting Schedule for 2012.....	21
2012 IRB Members.....	22

Institutional Review Board

Submission Requirements for New Protocol Review

1. **Principal Investigator's submitting Exempt studies (survey/questionnaires, record review, biological specimen collection & study of existing data) are not required to attend the IRB meeting. Only 1 copy should be submitted. Exempt studies that require informed consent Will Not receive expedited review & need to submit 22 copies Plus the original. It must go through full board review.**
 2. **Principal Investigator's submitting HUD studies Will Not receive exempt approval from the IRB Chair. Informed Consent is Not required for HUDs unless research information is being gathered to support a premarket application. Submit 22 copies Plus the original.**
 3. **Principal Investigator's submitting studies involving in-patients are required to attend or send a co-investigator/coordinator to the meeting to give a brief (5-10 minute) presentation of the protocol & answer questions from the Board. Submit 22 packets Plus the original (for FULL BOARD review)*.**
 - A. Each packet must contain:
 1. A Cover Letter from the Principal Investigator*
 2. A Brief Protocol Summary (2-5 pages)*
 3. The Study Protocol
 4. An FDA Approval Letter, IDE# or IND# (When applicable)
 5. FDA Form #1572 (When applicable)
 6. A Patient Informed Consent *, and Assent of a Minor Documents (projects involving minors from ages 7-17)*
- *These documents must be submitted on letterhead (cover letter & 1st page of informed consents) by 4:00 p.m. of the deadline date for submission (NO EXCEPTIONS).**
4. **Each copy Must be 3-hole punched.**
 5. **Do not staple, paper clip, or clip packets!!!**
 6. **Please make copies two (2) sided whenever possible.**
 7. **Submit a copy of the training certificate showing you have completed the NIH IRB Computer-Based Training (<http://phrp.nihtraining.com> , <http://citiprogram.org>) or the MCDH Protection from Research Risks educational program. *(If previous certificate completed is more than 2 years old, please retake the training course)***
 8. **Disclosure of any financial compensation by an outside source relating to the research study in the protocol summary and the informed consent.**

Institutional Review Board

Model Cover Letter

Date

Allan Naarden, MD
Chairman, Institutional Review Board
Medical City Dallas Hospital
12200 Park Central Dr., 1-Forest Ste. 500
Dallas, TX 75251

Re: Protocol Title

Dear Dr. Naarden:

I would like to submit the enclosed protocol dated _____, Patient Informed Consent dated _____, and FDA Form #1572 (*if applicable to your study*) for consideration by the Institutional Review Board at its meeting of _____.

_____ will be coordinating this protocol; please forward all correspondence to his/her attention.

This study is sponsored by _____.

If I can provide further information please do not hesitate to contact me. Your consideration in this matter is fully appreciated.

Sincerely,

Principle Investigator

Institutional Review Board

Protocol Summary Outline

Title:

Sponsor:

IND # or IDE # (if applicable)

Principal Investigator:

Associate or Co-Investigators:

- I. Background (why the study is necessary)
- II. Specific Aims of the Study
- III. Study Design (how the study will be accomplished)
- IV. Inclusion/Exclusion Criteria
- V. Recruitment of Patients
- VI. Potential Risks and Benefits
- VII. Special Precautions
- VIII. Financial Compensation by an Outside Source (e.g., do researchers or their family have a financial interest in the research project such as major stock holdings or funding from the sponsor?)
- IX. Hospital Departments/Services to be assessed by the Research

Institutional Review Board

BASIC ELEMENTS OF INFORMED CONSENT

(use this checklist to develop the informed consent document)

- A. An informed consent document must contain the following information and a copy must be provided to each patient.
- ___ 1. A statement that the study involves research. Note whether or not the patient will be informed about the results of the research study.
 - ___ 2. Identify any sponsor. Explain the relationship (if any) between the study doctor and the sponsor of the research study (e.g., financial compensation to the investigator.)
 - ___ 3. A lay language (7th-grade level) description of the research purpose.
 - ___ 4. An understandable (7th-grade level) description of procedures to be used.
 - ___ 5. The approximate number of patients involved in the study; justification for the exclusion of any particular group of subjects.
 - ___ 6. The expected time and duration of the Patient's participation.
 - ___ 7. A description of any reasonably foreseeable risks or discomforts to the patient (or to the embryo or fetus, if the patient is or may become pregnant); any requirement for contraception. In the case of drug use, a full and fair exposition of side effects must be given.
 - ___ 8. Identification of any experimental procedures.
 - ___ 9. A statement that there may be risks to participation in the study that are currently unknown.
 - ___ 10. Any costs to the patient that may result from participation in the research.
 - ___ 11. A statement of whether the process will require hospitalization.
 - ___ 12. For research involving more than minimal risk, an explanation as to whether any compensation is involved; and an explanation whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
 - ___ 13. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be available to the patient.
 - ___ 14. A description of any benefits to the patient or to others which may reasonably be expected from the research.
 - ___ 15. A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained. The patient should be made aware that the FDA may inspect records pertaining to their research. Add Health Information Disclosure Statement.

Institutional Review Board

- ___16. A statement that participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled.
- ___17. Indication that the patient may discontinue participation at any time without penalty, loss of benefits or legal rights to which that patient is otherwise entitled; the consequences of the Patient's decision to withdraw from the research (these cannot involve penalties for withdrawing) and procedures for orderly termination of participation by the patient; and a discussion of circumstances under which the Patient's participation may be terminated by the investigator without regard to the Patient's consent.
- ___18. A statement that significant new findings developed during the course of the research which may relate to the Patient's willingness to continue participation will be provided to the patient.
- ___19. A statement regarding receipt of a copy of the informed consent document after signatures are complete.
- ___20. Additional elements of consent for genetic studies (if applicable).
- ___21. **The following statement must be included: If you have any questions about the research or if you have any research related injuries, you may contact (specify the Name of the Investigator and the Telephone Number). If you have any questions about your rights as a research patient, you may contact C. Yvette King, CCRP, IRB Supervisor, North Texas Institutional Review Board at (972)566-6060.**

When abbreviations are to be used for brevity, e.g., CBC, EEG, EKG, the first use will be accompanied by the spelled out term in brackets.

Institutional Review Board

A Model Informed Consent

Page 2

The following procedures or drugs which will be used are experimental, (*list*).

Side Effects, Toxicities and Risks

The following risks, side effects or toxicities are possible (*explain in lay terms the risks which may occur to the patient, or to an embryo or fetus if patient becomes pregnant*).

In addition, these procedures (*or the use of drugs*) may involve risks to you which are currently unforeseeable.

Extraordinary Costs

The following additional charges will be made because of your participation in the study (*list, if any, otherwise remove this sentence*). (*Address the issue of compensation to the patient in this section.*) *You (will/will not) be paid for participating in this study.*

Your participation in this study will (*require, not require*) hospitalization. Unforeseen consequences of the experiment may require your hospitalization.

No funds for compensation for injuries associated with participation in this study have been set aside. (*Of, if treatment will be provided, explain instead of using the above sentence*). You are free to contact the below listed investigator if you have questions and you may report research related injury to that investigator or to the Institutional Review Board which reviewed this study.

Alternatives

The following procedures or courses of treatment are available as alternates to the research procedure. (*List any alternative procedures or treatments. If there are not any, so state in this area.*)

Benefits

The following are the direct and indirect benefits which you may derive from participation in this study (*list the benefits*).

Page ____ of ____ Pages

Institutional Review Board

A Model Informed Consent

Page 3

Confidentiality

Your records will be held confidential by all parties involved in this research study and you will not be identified in any publication. However, the Food and Drug Administration has the right to access your medical/research records and identity, and may have the need to release this information. (*List any other entities who may have access to research-related records.*) In addition, personal information may be disclosed if required by state or federal law.

Participation

Your being in this study is voluntary. You may refuse to be in the study without penalty to you or without loss of any treatment rights.

You may also leave the study at any time without penalty, loss of benefits or legal rights.

Under the following circumstances the investigator may need to end your being in this study. (*describe those circumstances*)

New Findings

You will be told of anything new learned during this study which could affect your willingness to continue being in the study. Your physician, the sponsor or the Institutional Review Board has the right to terminate the study based on this information.

Questions

You have a right to have all questions about the study answered in away that you clearly understand the answer.

If you have any questions about the research or if you have any research related injuries, you may contact (*specify the Name of the Investigator and the Telephone Number*). If you have any questions about your rights as a research patient, you may contact C. Yvette King, CCRP, CIM, IRB Supervisor, North Texas Institutional Review Board at Medical City Dallas at (972) 566-6060.

Page ____ of ____ Pages

Institutional Review Board

A Model Informed Consent

Page 4

Where Can I Get More Information?

(Do not include this section if your study is a phase I, major toxicity or device feasibility trial)

A description of this clinical trial will be available on <http://www.clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

You will receive a signed copy of this consent form.

I understand and am satisfied with the above information, and I acknowledge having received a copy of this consent form.

Patient Printed Name and Signature

Date

Witness Printed Name and Signature (if appropriate)

Date

Guardian Printed Name and Signature (if appropriate)

Date

Printed Name/Signature of Person Conducting Consent

Date

Institutional Review Board

Assent by Minors (7 - 17 years of age) to Voluntarily Participate in a Research Study

Any new research projects involving a minor as a volunteer patient will require the development and completion of age-specific documentation of assent as well as an informed consent document to be signed by the parent/guardian. Additionally, before any previously approved research projects involving minors as volunteer patients can be re-approved for continuation on an annual basis, an age-specific documentation of assent will need to be prepared in addition to the informed consent document signed by the parent/guardian.

“Assent” means the affirmative agreement of a minor to participate as a volunteer patient in a research project. The mere failure to object should not, in the absence of an actual affirmative agreement, be construed as assent. Following are general assent requirements by age groups (see attached age-specific Model Assent Documents):

Assent by Teens. In addition to the signed informed consent of their parent/guardian, the research project informed consent form should also contain a section for adolescents, thirteen (13) to seventeen (17) years of age, to acknowledge their assent to voluntarily participate in the study.

Assent by Pre-teens. In addition to a signed informed consent by the parent/guardian, a separate, age-appropriate assent form should be provided to children under thirteen (13) and over seven (7) years of age to acknowledge their assent to voluntarily participate in the study.

Waivers to Informed Assent. The IRB will consider waiving the requirement of informed assent upon request of the investigator. A waiver may be granted for those studies in which the investigator can demonstrate that requesting assent is not in the best interest of the minor due to the child’s lack of maturity, psychological state and/or physical state.

If you have any questions about these requirements, or if you need a copy of the entire IRB Policy and Procedures Manual, which more fully details all research requirements at MCDH, please contact either Yvette King, CCRP, CIM, IRB Supervisor at (972) 566-6060.

Institutional Review Board

ASSENT TO PARTICIPATE IN RESEARCH

(Ages 7 – 12 years old)

Study title: *[insert here]*

Doctor in charge of study: Dr. ___*[full name]*_____

We are asking you to be in a research study. You have to decide if this is OK. We want to know if a new way of treating your illness will work. We want you to be in this study because *[specify, e.g., you are sick, you have cancer, your heart pushes your blood too hard, your heart beats differently]*.

If you are in this study: *[edit/add text to complete description from child's point of view if needed]*.

1. We will check your health to make sure you can be in the study. We will take a little blood from your arm with a needle. We will give you a cream to put on your arm, so it will not hurt as much.
2. You will take a pill/medicine xx times a day, every day for xx months.
3. You will come to the doctor's office xx times.
4. You will go to the hospital xx times.
5. Each time you go to the doctor's office/hospital, we will take a little blood the same way as before *[or describe other testing, e.g., Each time you go to the hospital, you will have a needle stuck in your back to take out some fluid./ You will have a test where you lie on a table inside a big machine that takes pictures of your head.]*
6. The study will last about xx *[days/weeks/months/years]*.

If you are in this study, you will help us learn more about how to treat your illness. This might help other kids. Also, you might get better. But, we do not promise this.

Being in this study might make you feel worse. *[Specify in age-appropriate language, e.g., You might get a headache, have a rash, or throw up.]* You might have no bad effects. We do not know. If you do feel worse, we will try to help you as soon as possible.

You do not have to be in this study. If you do not want to be in the study, it is OK. We will treat you the same way as if we never asked.

If you decide to be in the study, you can change your mind later. You can quit any time.

Talk to your parents about the study. They also have to decide if it is OK for you to be in it. Ask all the questions you can think of. You can ask the doctor or your parents. You can ask questions at any time.

We will give you a copy of this form to keep.

Institutional Review Board

If you want to be in the study, write your name on the line.

Printed Patient Name and Signature

Date

I believe my child understands what will happen in this study and his/her signature shows that he/she agrees to be in the study.

Parent Printed Name and Signature

Date

Institutional Review Board

ASSENT TO PARTICIPATE IN RESEARCH

(Ages 13 - 17 years old)

Study title: *[insert here]*

Doctor in charge of study: Dr. ___*[full name]*_____

We are asking you to be in a research study. You must decide if you agree to be in this study. We are doing this study to *[describe what study is about in 7th grade language, e.g., find out if a new medicine works, find out if taking xx drug in a different amount works, find out if a new device helps you hear better]*. We want you to be in this study because *[specify reason for approaching patient, e.g., you have bone cancer, your heart beats differently, you have high blood pressure]*.

If you agree to be in this study, the following will happen to you: *[complete all that apply and add more if needed and specify from child's point of view, e.g.,]*

7. We will do a physical exam to make sure you should be in the study. We will take some blood from your arm with a needle.
8. You will take a pill/medicine xx times a day, every day for xx months.
9. You will visit the doctor's office xx times.
10. You will go to the hospital xx times.
11. Each time you go to the doctor's office/hospital, we will take a little blood. *(or describe other testing, e.g., Each time you go to the hospital, you will have a needle stuck in your spine to take out a fluid sample/ You will have 2 MRIs, in which you lie on a table inside a large tube that takes pictures of the inside of your body.)*
12. The study should last about xx *[days/weeks/months/years]*.

If you are in this study, you will help us learn more about how to treat your disorder. This might help other kids. The treatment we are studying also might help you, but we do not promise this.

The treatment or tests in this study might have side effects. *(Describe in age appropriate language, e.g., You might get a headache, have a rash, or throw up.)* You might have no side effects. We do not know. If you do experience side effects, we will try to make you feel better as soon as possible.

You do not have to be in this study. If you decide to participate, you can change your mind later. You can get out of the study at any time.

If you decide not to be in the study, there is no penalty. We will treat you the same way as if we never asked.

Discuss this study with your parents. They also have to decide whether you can be in it. Ask your parents or the doctor any questions you have about this study. If you have any questions later, you will have a chance to ask then also.

We will give you a copy of this form to keep.

Institutional Review Board

If you agree to participate, sign your name on the line below.

Patient Printed Name and Signature

Date

I believe my child understands what will happen in this study and his/her signature shows that he/she agrees to be in the study.

Parent Printed Name and Signature

Date

Institutional Review Board

PARENTAL WAIVER OF ASSENT

(For children 7 – 17 years of age)

I wish to waive obtaining my child's assent for joining this study because of his/her:

maturity_____

psychological state_____

physical state_____

I believe that the study is appropriate for my child and that his/her best interests are being served by not requiring his/her assent as a pre-requisite for joining this study.

Printed Name and Signature of Parent/Guardian

Date

I concur with the decision to waive assent for this patient for the reason(s) indicated above.

Printed Name and Signature of Principal Investigator

Date

Institutional Review Board

ADDITIONAL ELEMENTS OF CONSENT:

GENETIC STUDIES

Procedure

Information about you (your child) resulting from the tests on your (your child's) tissue will NOT be provided either to the study doctor or to you. This includes genetic information that may be relevant to your (your child's) prognosis or to treatment for your (your child's) cancer and any incidental findings regarding other disorders, risks of disease, or other characteristics that may be detected by genetic analysis.

Voluntary Participation (adult consent for child)

If your child reaches age 18 during this study, his/her consent will be sought to continue participation in this study.

Withdrawal

If you (your child) chose to withdraw from the study, your (your child's) tissue samples that are already in the tissue bank will stay there. No additional tissue samples or clinical information about you (your child) will be sent to the tissue bank. If you request it, the link between the data and you (your child) will be removed.

Risks

The only risk in this study is the potential loss of privacy with respect to your (your child's) genetic characteristics. We will try to protect your (your child's) privacy by using a code to identify all information that is sent to the tissue bank. We will retain information that links your (your child's) name to the code in the local doctor's office, so that follow-up data can be sent later and linked to earlier data.

In addition, a Certificate of Confidentiality has been obtained from the National Cancer Institute. This certificate prevents information gathered in this study from being disclosed in almost any case, such as a court subpoena or requests for information by an insurer. Information about you (your child) may still be reviewed by officials at the National Cancer Institute or other Federal agencies for legally allowed reviews of federally funded studies.

Institutional Review Board

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

You have a right to privacy. This means all information obtained as a part of this study will only be used as described below. The results of this study may be published in a scientific book or journal. If this is done, your name will not be used without your specific written permission. In addition, if photographs, audiotapes or videotapes are taken during the study, then you must give special written permission for their use. All information about you from this research project will be kept in a locked space.

By signing this Agreement you agree to allow (*put name of investigator here*) and his/her staff (Researchers) and the study sponsor, (*put name of sponsor here*) (Sponsor), to use and disclose health information that identifies you for the purposes described below. You also agree to permit Medical City Dallas Hospital, its staff, your doctors, and your other health care providers to disclose health information in your medical records to the Researchers and Sponsor for the purposes described below.

The Researchers and the Sponsor may use and share your health information to conduct the research. They may use your health information as described in the informed consent. They may disclose your health information as required by law and to representatives of government organizations, review boards, and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research.

If information that could be used to identify you has been removed, then the information that remains is no longer subject to this Authorization and may be used and disclosed by the Researchers and Sponsor as permitted by law. Once your health information has been disclosed to another party as indicated above, federal privacy laws may no longer protect it from further disclosure. However, the Researchers and Sponsor agree to protect your health information by using and disclosing it only as permitted by you in this Authorization. These limitations will continue even if you revoke (take back) your Authorization.

You do not have to give this permission and it is all right to refuse to sign this section of the consent form. Your doctor will still treat you even if you do not give your permission for this release of information. Your insurance will still pay your medical bills if you do not give your permission. However, since it is important for the people listed above to have access to your information, if you do not sign this Agreement, you cannot be in the research study.

While the research is in progress, you will not be allowed to see any health information that is created or collected. After the research is finished, you may see the information if you wish. Unless permission is specifically withdrawn, this permission will NOT expire at the end of the research study.

You will be given a copy of this Authorization after you have signed it.

Signature of Patient

Date

Printed Name of Patient

Institutional Review Board

AFTER APPROVAL REQUIREMENTS

Once your protocol has been approved by the IRB and you begin your study, you will still need to observe the following paperwork requirements:

1. Informed Consent. Written consent must be obtained from all subjects in your study and a copy of the signed consent must be given to the patient. You should keep the original copy of the signed and witnessed consent form in your records of the protocol for a period of three years past completion of the study. Also, you must put a copy of the signed consent form in the subject's medical records and make a note that the consent was obtained prior to entrance of the patient into the study. If this is an inpatient study, be sure the Ward personnel are aware of the study requirements. Changes to the consent form must be reviewed and approved by the IRB before the new informed consent can be used in the study. Re-consenting of the patient if the change significantly impacts future risks or benefits for having entered the trial, or if the sponsor requires formal re-consent. Otherwise, letters of information to the subject suffice since they can be informed without having to return to the clinic.

2. Adverse Events. You must promptly notify the IRB of all adverse events and protocol deviations that occur to patients you have enrolled in this study. Serious adverse event (long-lasting or irreversible damage to human health, partial or complete impairment of bodily functions, impairment of normal activity by all/most persons exposed at one time/each time an individual is exposed) notifications should be submitted to the IRB within 10 days of occurrence. Also, you must promptly provide the IRB with a copy of any adverse event or safety reports sent to you by the study sponsor.

3. Amendments. You must notify the IRB in writing of any amendments or other changes to the protocol. These changes must be approved by the IRB before you can institute them in the study.

4. Reports. You must provide a periodic interim/annual reports to the IRB. The IRB will notify you when your report is due. If you do not provide the requested report, the IRB may administratively close your protocol. Also, when your study is completed or is closed, you must provide a final report to the committee and notify all your sub-investigators.

North Texas Institutional Review Board at Medical City (IRB)

7777 Forest Lane, 1-Forest, Dallas, TX 75251 Phone 972/566-6060 Fax 972/566-4715

2012 Meeting Schedule 12:00 p.m.-1:00 p.m./MCCH Boardroom

<u>Meeting Date</u>	<u>Deadline for Submission</u>
January 18	January 6
February 15	February 3
March 21	March 9
April 18	April 6
May 16	May 4
June 20	June 8
July 18	July 6
August 15	August 3
September 19	September 7
October 17	October 5
November 21	November 9
December 19	December 7

Meetings will begin at 12:00 p.m. and run through 1:00 p.m.

All documentation for new study consideration and active protocol updates must be submitted by the deadline or it will be placed on the following months' agenda.

Mail all Correspondence to:
Yvette King, CCRP, CIM
Supervisor, Institutional Review Board
Department of Clinical Research
Medical City Dallas Hospital, 1-Forest
12200 Park Central Dr., Ste 500
Dallas, TX 75251

For assistance contact Yvette King at (972) 566-6060

01/12

**North Texas Institutional Review
Board at Medical City (IRB)
2012 Committee Members**

- *Allan Naarden, MD, Chairman, (Neurology, 1-Forest Ste. 500, Ph 972/566-4718) (10/85)
Rebecca Brakke, BA, (Non-Inst. Member, 7027 Eudora, Dallas, TX 75230, Ph 214/363-0921) (4/96)
*Brian Cohen, MD, (Reproductive Endocrinology, C-625, Ph 972/566-6686) (01/05)
Leah Domstead, Esq, (Attorney, 13355 Noel Rd., Ste 650, Dallas, TX 75240, Ph 972/789-2833) (8/99)
*Deborah Echtenkamp, RN, (Pedi Hem/Onc., D-6th Floor, Ph 972/566-7367) (10/03)
*Deji Fashemo, DDS (Orthodontics/Craniofacial Orthopedics, C-770, Ph 972/566-3100) (1/12)
Ken Glass, MD, (Non-Inst. Member, 3521 Cornell Ave., Dallas, TX 75205, Ph 214/522-3953) (1/06)
*Carol Gregory, RN, MSN, MBA, NEA-BC (Chief Nursing Officer, A-240, Ph 972/566-6938) (10/11)
Betty Hayes, (Non-Inst. Member, 7437 Malabar, Dallas, TX 75230, Ph 214/363-5741) (9/05)
*Carl Lenarsky, MD, (Pediatric Hematology/Oncology, Ste. D-400, Ph 972/566-4449) (1/98)
Michael Lorfing, MFS, (Non-Scientific & Non Institutional Member, Ph 972/566-6782) (03/09)
Hema Sawhney, MLS, (Non-Scientific Member, Librarian, Bldg. A 2nd Floor, Ph 972/566-7579)
(03/09)
*John Nemunaitis, MD, (Oncology, Mary Crowley Cancer Research Centers, 1700 Pacific Avenue,
Suite 1100, Dallas, TX 75201, Ph 214/658-1993) (01/10)
Jim Poole, ThM (Clergy, Ste. A-140, Ph 972/566-7584) (10/09)
*Ruben Saez, MD, (Hematology/Oncology, Ste. C-204, Ph 214/483-6933) (01/10)
*Michael Savin, MD, (Hematology/Oncology, Suite D-400, Ph 972/566-7790) (9/98)
*Matthew Trovato, MD (Pediatric Plastic/Craniofacial Surgery, B-300, Ph 469/375-3838) (1/12)

***Alternate For Scientific Members**

- Armand Derousseau, Pharm D., (Pharmacy Director, Ste. A-177, Ph 972/566-8251) (9/01)
Bruce Bowers, MD, (Cardiovascular Disease, Ste., C-339, Ph 972/566-8855) (01/12)

IRB Supervisor/Recorder

- C. Yvette King, BS, CCRP, CIM (Supervisor, Clinical Research, 1-Forest, Ste. 500, Ph. 972/566-6060)
(01/12)

IRB Glossary

Administratively Closed

Administrative decision of the IRB based on PI non-responsiveness to IRB requests. This can occur prior to initial IRB approval or any time following IRB approval.

Adverse Event (AE)

Any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment.

Approval

The IRB has reviewed the protocol/informed consents and feels the investigator has undertaken every effort to minimize risk to the subjects, the research plan makes adequate provision for monitoring the safety of the patients, were satisfied with the investigator's provision for subject privacy and confidentiality, found recruitment of potential subjects to be equitable, feel that proper informed consent/assent would be obtained from each subject as appropriate prior to their enrollment in the study and finally that the investigator's methods safeguarded the rights of vulnerable subjects.

Assent

Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research. Mere failure to object to the research may not be construed as assent.

Assurance

A formal written, binding commitment that is submitted to a federal agency in which an entity promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved.

- **Federal-Wide Assurance (FWA)** An agreement between a federally funded entity and OHRP that stipulates methods by which the entity will protect research participants.

Audit

A system to assess protocol compliance with and adherence to the Federal regulations and guidelines. Periodically, IRB records for the selected protocols may be reviewed to capture the initial IRB approval date, dates of renewal, occurrences of adverse events and, if applicable, lapses of IRB approval.

Benefit

A valued or desired outcome; an advantage.

Beneficence

An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

Children

Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted. A formal assent is required before children participate in research.

Clinical Trial

A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.

Cognitively Impaired

Having either a psychiatric disorder (*e.g.*, psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (*e.g.*, mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

Competence

Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice.

Compliance

Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory and institutional requirements.

Confidentiality

Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

Continuing Review

Periodic review of a research study by an IRB to evaluate whether risks to participants are reasonable in relation to potential benefits and to verify that the study continues to meet regulatory and institutional requirements. Continuing review shall be conducted at intervals appropriate to the degree of risk but not less than once per year.

Data and Safety Monitoring Board

A committee of scientists, physicians, statisticians, and others that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

Deviation

Any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control & that has not been approved by the IRB.

Drug

Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

Entity

An organization, institution or being that has its own existence for legal or tax purposes and possess OHRP-approved Assurances.

Exempt Research

Research determined by the Institutional Review Board (IRB) to involve human subjects only in activities involving minimal risk (i.e. surveys, data collection, retrospective chart review).

Expedited Review

Review of proposed research by the IRB chair or a designated voting member rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research (i.e. Exempt Studies).

Experimental

Term often used to denote a therapy (drug, device, procedure) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal study (research) to evaluate its usefulness.

FDA

Food and Drug Administration; an agency of the federal government established by Congress in 1912 and presently part of the Department of Health and Human Services.

Full Board Review

Review of proposed research at a convened meeting at which a majority of the voting membership of the IRB is present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

Grant

Financial support provided for research study designed and proposed by the Principal Investigator(s).

The granting agency exercises no direct control over the conduct of approved research supported by a grant.

Guardian

An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care.

HIPAA

Health Insurance Portability and Accountability Act of 1996. This mandates the maintenance of privacy for a subjects' personal information.

Human Subjects

Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations, human subjects are defined as: living individual(s) about whom an investigator conducting research obtains; (1) data through intervention or interaction with the individual; or (2) identifiable private information.

Incapacity

Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence. See also

Incompetence

Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

Informed Consent

A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the entity or agents thereof from liability for negligence.

Institutional Review Board (IRB)

A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research.

Investigational Device Exemptions (IDE)

Exemptions from certain regulations found in the Medical Device Amendments that allow shipment of unapproved devices for use in clinical investigations.

Investigational New Drug or Device

A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing.

Investigational Product

A device or pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

IRB Records

IRB records include but are not limited to: all minutes of IRB meetings, a copy of all proposals reviewed including all amendments, investigator brochures, and any supplemental information including recruitment and informational materials, consent forms, information submitted for continuing review, all correspondence, and IRB membership with a resume for each member.

Justice

An ethical principle discussed in the Belmont Report requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.

Legally Authorized Representative

An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Medical Device

A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

Minimal Risk

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 the participant's daily life or during the performance of routine physical or psychological examinations or tests. In research involving prisoners, minimal risk is also defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Monitoring

The collection and analysis of data as the project progresses to assure the appropriateness of the research, its design and subject protections.

Non-Affiliated Member

Member of an Institutional Review Board who has no ties to the parent entity, its staff, or faculty. This individual is usually from the local community (*e.g.*, minister, business person, attorney, teacher, homemaker).

Office for Human Research Protections (OHRP)

The office within the U.S. Department of Health and Human Services, responsible for implementing DHHS regulations governing research involving human subjects.

Permission

Parent(s) or guardian's written agreement to the participation of their child or ward in research.

Principal Investigator (PI)

The scientist or scholar with ultimate responsibility for the design and conduct of a research project.

Protocol

The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

Quorum

A quorum is defined as a majority of the voting members appointed to the IRB membership. In the case of the IRB, a quorum must include at least one member whose primary concerns are in non-scientific areas. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

Request for Additional Information

The IRB has reviewed the study and has requested changes or clarifications.

Research

Systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Retrospective Studies

Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case control studies are an example of this type of research.

Risk

The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk".

Serious Adverse Event (SAE)

A SAE is defined as death; a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.

Sponsor

A person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator) and the employees are considered to be investigators.

Study

All components of a research project.

Study Closure

Study approved by the IRB can be closed by the investigator, the sponsor, the IRB,

Suspension/Termination

IRB approval is suspended/terminated and all research activity halted as the result of unanticipated problems involving risks to subjects or others; serious or continuing noncompliance with or the requirements or determinations of the IRB.

Survey

Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

Tabled

The IRB has reviewed the study and determined that extensive changes are necessary. The study will be re-reviewed once changes have been made.

Unexpected Adverse Event

An UAE is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.

Violation

A deviation from the IRB approved protocol that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data.

Voluntary

Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate(or to continue to participate) in a research activity.

MCDH EDUCATION PACKET & TEST

(on following pages)

Be sure to either:

**fax:[972]-566-4715, mail or bring answer sheet to the Clinical Research Department [12200 Park Central Dr., 1-Forest Ste. 500, Dallas, TX 75251]*

Research Protection Background

Scientific progress and changes in the relationship between science and society are creating new challenges for the scientific community. Ethics in the conduct of research is more closely monitored and regulated than it was in the past. The part played by science in society has become more prominent and more complex, with consequences that are both invigorating and demanding.

It is important that the clinical investigator ensure that the rights and welfare of human subjects be adequately protected. The current system for the protection of the human participants in research dates from the work of the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**, established in 1974, in response to the revelation of researcher misconduct in such trials as the Public Health Service Study of Untreated Syphilis in Black Males conducted at the Tuskegee Institute. A specific example known for its notoriety, this study involved a targeted black male population being tracked over the decades to find out the natural course of untreated syphilis. The public outrage when this study became publicized led directly to the formation of the **National Commission** (June 1974) and the initial publication of **45 Code of Federal Regulations 46** (45 CFR 46: Protection of Human Subjects) by the Department of Health Education and Welfare (May 1974). The regulations continue in revised form to govern the review and performance of clinical research supported by the Department of Health and Human Services.

The charge to the National Commission was to identify the basic ethical principles that underlie the conduct of human research and to develop guidelines to assure that human research is conducted in accordance with ethical principles. The National Commission produced several reports, two of which are of particular interest to researchers. **The Belmont Report**, published in 1979, was named after the conference center at which the Commission deliberated; it outlined the ethical principles that serve as the moral foundation for our system of protections for human research participants. **The Report and Recommendations: Research Involving Children**, published in 1977, established the important concepts of minimal risk[‡], parental permission and child assent that are central to the additional protections afforded children who participate in research.

The incident at the Tuskegee Institute was not the only turning point that led to the development of research ethics inclined towards the protection of human research participants. In 1946, renowned German Nazi physicians and administrators were put on trial, then known as the Nuremberg War Crime Trials, for their willing participation in the merciless killing of those deemed “unworthy of life” and the performance of crippling and deadly medical experiments on thousands of concentration camp prisoners.

[‡] **Minimal risk** is the probability and magnitude of physical or psychological harm that is normally encountered in daily lives, or in routine medical or psychological examination.

The judge's verdict in August 1947 included a section called "Permissible Medical Experiments" which became known as the **Nuremberg Code**. Although never adopted into either German or American law, the Nuremberg Code continues to inform and influence the pattern of the development of international ethics statements. In essence, the Nuremberg Code was the first widely recognized document to deal explicitly with issue of informed consent and served as the first systematic statement of the professional ethic for medical researchers. This code was reflected in the Declaration of Human Rights and accepted in principle by each of the 51 original signatory nations of the Charter of the United Nations.

The World Medical Association adapted the Nuremberg Code to the needs of the biomedical community, producing the first version of the **Declaration of Helsinki** in 1964. The Declaration of Helsinki has been revised five times, with the most recent meeting of the organization on October 2000. Included among the 32 principles is a requirement for the experimental protocol to be "...submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, or the sponsor...". The Declaration also recommends that research that was not performed "in accordance with [these] principles...should not be accepted for publication."

The Belmont Report, in contrast to the Nuremberg Code and The Declaration of Helsinki, which comprise of rules and guidances, serves and establishes as the ethical foundation for the practice and regulation of clinical research. The Report distinguishes between medical practice and research in order to "know what activities ought to undergo review for the protection of human subjects of research." Various criteria have been proposed to differentiate medical practice from research, such as the intent to publish or the use of research techniques such as randomization. Even though the dissimilarity between medical practice and research can be difficult to make, and the judgement as to whether a given activity constitutes research is often complex, it establishes the responsibility of the clinical investigator to submit research activity for review by an **Institutional Review Board (IRB)**.

The Commission discusses three basic principles in the Report that are "among those generally accepted in our cultural tradition" and relevant to resolve ethical dilemmas stemming from research involving human participants: the principles of respect for persons, beneficence and justice. The principle of **respect for persons** is based upon the ethical premise that an individual has certain rights to autonomy; furthermore, persons with diminished autonomy are also entitled to additional protection. Clearly, the respect for persons requires seeking the informed consent of the individual to participate in research. The National Commission identified three elements to informed consent; that is, sufficient information for the volunteer to evaluate the research, the presentation of this information so that the potential volunteer can comprehend and make the informed choice, and conditions that are "free of coercion and undue influence". The Belmont Report incorporates under the principle of "respect for persons" the requirement to protect those persons with diminished autonomy. Hence, there are special protections in the federal regulations for the involvement of prisoners and children in research.

Accordingly, this right of autonomy or self-determination serves as the moral foundation for the procedural requirements of informed consent, assent, and permission.

The principle of **beneficence** is understood as an obligation to act in accordance with the participant's well being through avoiding harm, maximizing possible benefits and minimizing possible harms or risk. The application of the principle of beneficence includes proper research design, evaluating the competence of investigators to minimize risk and determining that the research provides a favorable balance of risk and benefit. An assessment of risks and benefits includes both the probability and the severity of the possible harm and anticipated benefits. The National Commission recognized that this assessment includes psychological, physical, legal, social and economic harm.

The principle of **justice** refers to the sense of "fairness in distribution" or "what is deserved". It requires us to ask about who receives the benefits of research and bears its burdens. The principle of justice also requires that a person not be denied a benefit to which they are otherwise entitled to without good reason. The National Commission recognized that the benefits of publicly funded research should be available to all.

The three basic ethical principles of respect for persons, beneficence, and justice serve as the moral foundation for the review and conduct of clinical research involving human participants. Respect for persons requires attention to the informed consent, surrogate permission, assent, maximization of choice, the protection of privacy, confidentiality and of vulnerable populations. Beneficence requires an examination of the experimental design, evaluation of the risk and benefit of the research, minimization of the risks of research participation, and the qualifications of the principal investigator. Justice requires attention to participant recruitment, the equal distribution of the burdens and benefits of research, and the inclusion and exclusion criteria for selecting participants. Lastly, an Institutional Review Board must determine the viability of a clinical trial and decide whether it is justified to provide therapeutic merits to the medical community.

The Informed Consent

The morality that has influenced the conduct of clinical investigation stemmed from the respect for persons, beneficence and justice. The rationale behind the informed consent is to provide the patient unprejudiced, accurate information necessary to weigh in the personal costs and benefits of participating in a research trial; it directly reflects the principle of respect for persons. The patient, upon agreement to an informed consent to participate in a patient oriented research, freely partakes in an investigation containing experimental procedures that the patient clearly understands. A patient who “provides informed consent” has voluntarily agreed to participate in research only after assessing the advantages and costs of their involvement in the procedure compared to other available alternatives. When obtaining the informed consent, the investigator should not only encompass essential elements in the consent but also answers the patient’s questions and listens to comments and concerns. This verbal exchange between patient and investigator is significant in ensuring that the patient fully comprehends the requirements and any consequences of research participation. The responsible clinical investigator should be aware of the following principles and has the following goals during the administration of the informed consent:

1. ***Clinical Investigators protect the subject’s autonomy.***
Subject participation in research must be voluntary. It is the investigator’s responsibility to avoid influencing or persuading the patient to participate or convince them not to participate.
2. ***Clinical Investigators assure that the patient comprehends the consequences and feasibility of research participation.***
The patient must be able to demonstrate to the investigator his or her comprehension of the consent, the addressing of any concerns and the likelihood of participation.
3. ***Clinical Investigators consider any aspects of the patient’s condition, disorder, disease, or demographics that might compromise his or her ability to process and analyze the information presented.***
The investigator modifies typical procedures to decrease influence of these factors on the informed consent process. Involving a relative, family member or significant other will help the patient alleviate any concerns and help them determine if participating in a study trial is in their best interest. It is essential to provide the patient such advocacy to compensate for issues that may impede their ability to provide informed consent.

4. ***Clinical investigators assume responsibility for the human subject's welfare, during and after the first encounter involving informed consent.***

The investigator is responsible for the patient's welfare throughout this entire process.

5. ***A practical consequence of a valid informed consent is that it is consistent with good research and societal support for research.***

The informed consent and subject compliance with a research protocol are related in that when a patient elects to fully participate in the informed consent process, they understand that their participation requires and are most likely to comply with the research protocol. The IRB decides whether a research study is fit to be approved and conducted.

Before presenting the informed consent to the patient, the investigator needs to confirm if the patient has the ability to read. The comprehension level of the consent form should not be higher than 7th grade level; the content must be presented in layman's terms as much as possible. Non-English speaking participants require a consent form written in their native language or, as an alternative, an interpreter be made available. Due to the many technical terms used in the consent, these are best defined in the language patients use daily and be conveyed to the patient in the best way the investigator sees fit. Undoubtedly, informed consent forms need to be simple and well organized for the patient's benefit. Several of the basic elements that comprise a consent form are as follows:

1. ***The Header and the Invitation To Participate:*** Includes the name(s) of the institution where the study will be conducted, the Principal and Sub Investigators and their contact information, emergency numbers, the title of the study protocol, the sponsor of the study and other identifiers. The invitation includes a definition of what 'research' is and distinguishes research from 'standard practice'[‡]. Background information is provided to outline the purpose of the subject's participation, the history of the research trial in question and other aspects such as the inclusion/exclusion criteria and diagnostic screenings. In recruiting and screening, the

[‡] *Patient-oriented research* can be defined as the systematic collection of information about new evaluations and treatment methods. The purpose of patient oriented research is to add new knowledge and improve clinical methods. Whereas *standard practice* can be defined as applying treatment methods used by practitioners generally. The purpose of standard practice is to select from the available options of treatments which best suits the individual.

investigator's goal is to develop a patient sample that is representative of a population into which generalizations will be made when findings are interpreted.

2. *The Purpose of the Study, Experimental Procedures and Alternatives to Research Participation:* This section of the consent form provides a concise description of the aim of the investigation or the research question under the study and also summarizes why the study is significant in improving public health. Experimental Procedures list all procedures in which subjects will participate and differentiate those which are experimental from those involved in standard care. An obvious alternative to research participation, of course, is refusal to participate. The investigator makes information on alternatives to participation available should the patient decline to consent.
3. *Risks, Costs and Benefits:* Risks fall into foreseen and unforeseen (e.g., to an unborn child) and the first step should be to identify the procedures that will involve some risk or discomfort. The risks discussed in the consent form are risks known to be associated with research procedures and should be differentiated from risks of conventional care. Examples include side effects of investigational medications, new diagnostic procedures and use of placebos. Before electing to participate, the patient needs to understand the financial effects of a research study. Usually, patients are not charged for the cost of experimental trials. Some study sponsors may pay for all, if not only some, of the experimental and standard procedures. The consent form identifies the procedures for which the patient will be charged and those that the patient will receive at no charge as part of the study participation. Research trials can be designed to provide benefit to only the participants, society or neither. An important judgement of the IRB is to evaluate the "cost-benefit ratio" of the research. The IRB will disapprove research with no benefit and will approve research that benefits both the participants and society, and has few, if any costs to either. During the informed consent process, the investigator must ensure that the patient has the autonomy, comprehension and resources to assess their own cost-benefit ratio.
4. *Agreement: Voluntary Participation and Withdrawal:* Voluntary participation is the essence behind the informed consent. The consent form contains a statement that the patient has the right to discontinue participation at *any* time. On the other hand, investigators and the sponsors also have the right to withdraw a patient from a study, when deemed necessary or participation becomes unsafe, without the patient's consent.

5. *Subject Rights to Confidentiality, Comprehension and Compensation (if applicable)*: The purpose of the Confidentiality section is to inform the patient of the extent to which data or specimens they have provided will remain confidential. The investigator also notifies the patient of the limitations on confidentiality that can arise when and if the FDA or IRB personnel review the study records. Patients are also advised that the results of the research will be submitted for publication and will not provide information that may reveal their personal identity. In an attempt to enhance recruiting or to promote compliance with the research protocol and its procedures, researchers may opt to pay the participants. Payments may be monetary or be something that the patient perceives as valuable (e.g., movie tickets); however, these payments should not be as valuable so as to coerce the patient into participating. The patient may also be reimbursed for their time and effort being a volunteer subject. Compensation may also be provided if a patient is injured while participating in a study. Contact numbers of the study investigator and the IRB must be provided within the consent form should the patient experience a research related injury, have additional questions regarding the study or their research rights. Although institutions are not required to provide care or payment for research injuries, procedures for reducing cost of research related injuries, like providing hospitalization and necessary medical care in emergency cases, may be implemented. Research subjects may not be asked to waive (or appear to waive) any of their legal rights in an informed consent. That is, the document may not contain exculpatory language.

The Informed Consent is one of the foremost ethical requirements underpinning research with human subjects; it reflects the basic principle of the respect for persons. It is not a single event; rather, a continuous process. Since subjects always retain the right to withdraw from a research, their continuing consent is important. This also assures that subjects will understand the nature of the research and can capably and *voluntarily* decide whether to participate.

HIPAA Privacy Rule

The Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), as codified at 42 U.S.C. Section 1320d, establishes the conditions under which protected health information (PHI) can be used or disclosed for research purposes. The Privacy Rule protects the privacy of individually identifiable health information, while at the same time ensures that researchers continue to have access to medical information necessary to conduct vital research. In the course of conducting research, researchers may create, use and/or disclose individually identifiable health information either with individual authorization (informed consent) or with an IRB waiver. Health information that may be considered individually identifiable includes such elements as: name, addresses, telephone numbers, e-mail addresses, birth date, social security number, medical record number, health plan beneficiary number, finger or voice prints, photographic images, names of relatives, and any other unique identifying number, characteristic, or code.

1. *Research Use/Disclosure of PHI With Individual Authorization.* A researcher may use and disclose PHI for research purposes when the research protocol has received IRB review and approval, and the research participant authorizes the use or disclosure of the information through a signed informed consent document.

2. *Research Use/Disclosure of PHI Without Authorization.* To use or disclose PHI without authorization by the research participant, the researcher must obtain a waiver from the IRB. To authorize the waiver, the IRB must determine that the use or disclosure of PHI involves no more than minimal risk to the individuals; the privacy rights and welfare of the individuals will not be adversely affected; the research could not practicably be conducted without the waiver; the research could not practicably be conducted without access to and use of the PHI; the privacy risks to the individuals are reasonable in relation to the anticipated benefits; there is an adequate plan to protect the identifiers from improper use and disclosure; there is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research; and there are adequate written assurances that the PHI will not be used or disclosed to any other person or entity except as required by law.

The IRB

Since its inception in 1964, The Declaration of Helsinki has been modified five times and among the 32 principles is a requirement for the investigational protocol to be reviewed by a “specially appointed committee independent of the investigator and the sponsor”. This was the beginning of the research review mechanism—The Institutional Review Board or IRB—that is now fundamental to the current system of human subject protections in the United States. The function of the IRB is the protection of human participants’ rights and welfare in research and assuring that risks are minimized to the extent possible: the focal point being the Federal Regulations governing research activity. These regulations include 45 CFR 46 (Protection of Human Subjects), 21 CFR 56 (Institutional Review Boards), and 21 CFR 50 (Protection of Human Subjects). As required by the Regulations, the IRB’s are composed of members with expertise in science, ethics, and non-scientific areas. Membership must be diverse (include consideration of race, gender, and cultural background) and sensitive to community standards. In addition, each IRB must include at least one member who is not otherwise affiliated with the institution (e.g., the non-institutional member). This diversity fosters a comprehensive approach to safeguarding patient rights and welfare.

Before the IRB can review a research project the investigator must provide the committee complete information regarding experimental design, the scientific rationale underlying the proposed research, a description of their plans for analyzing the data during the collection process, and the statistical bias for the structure of the investigation. The IRB should also determine at this point if the investigator is competent in the area being studied and whether investigators serve *dual roles* (e.g., treating physician, teacher, or employer in addition to being a researcher) that might complicate their interactions with the subjects. To minimize further risks, the IRB must also assess whether the research design will yield useful data, determine the beneficial and harmful effects anticipated in the research and if adequate safeguards are incorporated within that design. When the sample size is too small to yield valid conclusions or the hypothesis is poorly formulated, subjects may be exposed to unnecessary risk. Poor or faulty research designs mean that risks are not likely to be reasonable in relation to the benefits.

When the committee reviews the study protocol in question, several aspects are taken into consideration:

- *Basic Ethical Principles.* The IRB shall review human research protocols in accordance with the basic ethical principles set forth in the ***Belmont Report***. These three relevant principles are the *Respect for Persons*, *Beneficence* and *Justice*. The design of the study must be consistent with sound scientific principles.
- *Informed Consent/Assent.* Again, ethical principles take into consideration the elements of informed consent/assent, sufficient information about the nature and effect of research and the

comprehension of the subject. The committee must look at risks, even when unavoidable, that can be reduced or managed. Precautions and safeguards can be incorporated into the research activity to reduce the probability of harm or limit its severity or duration.

- *Committee Decisions.* The committee will review and discuss the protocol in question, vote accordingly for and denote the protocol as *Full Approval*, *Approval with Required Revisions*, *Deferral* (if the committee does not have the expertise to reach a decision and needs to involve a consultant) or *Disapproval*. Final decisions on all proposals are made with the committee involved as a whole.
- *Protocol Changes.* Minor changes in the research protocol or informed consent/assent may be approved by expedited review by the chairperson and/or a designee. If the proposed change is major then the full committee must review and approve the proposed change. The IRB shall be promptly informed of the change and should review the change in the study to determine that it is, in fact, consistent with ensuring the continued welfare of the research subjects.

The Federal Regulations' 45 CFR 46.111 indicate detailed criteria that an IRB must use in approving research. Regardless if the IRB uses an expedited or full review method, the research must satisfy the following requirements:

- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of the subjects.
- Selection of subjects is equitable. The IRB should take into account the purposes of the research and the setting in which the research would be conducted. Current rules (45 CFR 46, Subpart B) require that women be included in research studies, unless their exclusion can be fully justified so that research findings can be generalizable and of benefit to all persons at risk of a disease.
- The risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk and, if appropriate, using procedures already being performed on the subjects for diagnostic purposes.

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

An IRB's evaluation of the risk-benefit ratio is the major ethical judgement that is made during this approval process. It is a judgment that often depends upon prevailing community standards and subjective determinations of risks and benefit. The degree of the risk posed by the research must be relative to the level of monitoring in the research plan. This monitoring process determines if information generated from the trials should be passed on to the subjects, alter the ratio of risk and benefits or lead to modification of evaluated treatments. Many multicenter and double-blinded studies have independent safety monitoring boards that fulfill this same function. They decide if and when the data are sufficiently favorable to one treatment that the study should be discontinued, which sometimes occurs sooner than investigators had planned.

There are additional requirements that must be met if the research involves prisoners or children, the so-called "vulnerable populations". Vulnerable populations are those individuals who may be especially vulnerable to coercion or undue influence or may not be able to provide consent. Federal regulations require that special consideration be employed in research with these populations. These requirements are defined under 45 CFR 46, Subpart C and Subpart D, respectively. The investigator should contact the IRB to discuss procedures concerning Subpart C requirements. As for children, research that does not offer the prospect of direct benefit is restricted either to minimal risk research or to research that involves only a minor increase over minimal risk. Research, which offers the prospect of direct benefit to the individual child, may involve greater than minimal risk, provided that the risk is justified by the anticipated benefit to the child and the relation of the anticipated benefit to the risk is at least favorable to the child as that presented by alternative approaches (45 CFR 46.405).

Hence, through the methods and ideals set forth by the IRB, human participants in medical research are not subjected to maltreatment and abuse. The ability to conduct human research is a privilege granted to the scientific community by the trust of the participants and society; enforcing proper ethical standards is one of the key means that subjects are ensured that their rights are not violated.

Good Clinical Practice

The Good Clinical Practice (GCP) standard developed by the International Conference on Harmonization (ICH) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the safety and well being of trial subjects are protected, consistent with the principles that have their origin within the Declaration of Helsinki. Any investigator performing a clinical trial involving a drug, biologic or device must conduct the trial in compliance with the Good Clinical Practice standard.

The ICH/GCP principles describe what is expected of the investigator conducting clinical trials. These responsibilities include:

- Meeting the qualifications required of the trial in terms of education, training and experience;
- Being thoroughly familiar with the investigational product under study;
- Being open to review by both the sponsor of the trial and the appropriate regulatory entity;
- Having the appropriate resources, including the suitable subjects, available time to conduct the study, and adequate staff support.

Before the start of a trial, an investigator needs to acquire approval from the IRB. This requires the submission of protocol detailing the trial, the proposed Informed Consent form, recruitment information, and proof of education in the responsible conduct of research. The sponsor of the study provides an investigator's brochure to the IRB as well as other updates to the trial. Once approved, the investigator follows the protocol as agreed to by the sponsor and investigator. Since the obtaining of the informed consent is central to any type of human research study, it must be conducted in a manner to ensure that the subject has good comprehension on what he/she is going to be participating in.

Drug accountability is an important part of the investigator's responsibilities. Records of drug receipt from the sponsor, dispensing information and the return of unused drug are essential. The preferred practice is to have a pharmacist maintain these records and be in charge of storage and dispensing. Many clinical trials include randomized treatments and single or double-blind designs. The investigator should follow the procedures for randomization described in the protocol. The sponsor or an individual (e.g., the pharmacist) may control the randomization schedule. The blinded condition of the trial should not be broken except when warranted for subject safety. If the blinding is broken, it needs to be documented and the sponsor notified.

The investigator is also responsible for the maintenance of written records and source documents. The record keeping must be accurate, complete, and reported on time to the sponsor. Any type of record modification to a document has to be dated and signed. Another concern during the research is safety. Serious adverse events (SAE) must be reported immediately to the sponsor as well as the IRB, and, if necessary, the FDA. On occasions, a trial may be suspended or terminated unexpectedly before the proposed end date. The investigator is responsible to inform the subjects and assure them that appropriate treatment is available. Notification to the IRB and the appropriate regulatory agencies should be done promptly. Once a trial is complete, a final study report is sent to the sponsor and also to the IRB for study closure.

These responsibilities are relevant for all types of clinical trials that fall under the ICH/GCP standards. In protocol development, investigator-initiated protocols are submitted to a company or the government for funding consideration; while in industry sponsored trials, the protocol is usually written beforehand prior to approaching the investigator to participate. Regardless of the origin of the protocol, specific elements should be considered in the development.

1. *Purpose:* A statement of the study objectives.
2. *Background:* A brief review of the state of development of the drug, device or concepts to be studied. Also includes the results of preclinical studies that have clinical significance.
3. *Concise Summary of the Project:* A brief description of the proposed study written at a “layman’s” language level. Describes the treatment design to be conducted (double-blind, placebo-controlled, etc.) Also describes the method of randomization and/or blinding, if applicable.
4. *Treatment of Subjects:* Identify the treatments to be administered, including the name of all drugs, the dosage(s), treatment schedule, the route of administration, period of treatment and follow-up.
5. *Criteria for the Inclusion of Subjects:* A description of the characteristics of the subject population and the inclusion criteria and an explanation of the rationale for the use of the subjects who are considered vulnerable.
6. *Criteria for Exclusion:* A description of the characteristics that would exclude a person from study inclusion and justification for the exclusion where appropriate.
7. *Sources of Research Material:* Identification of the sources of the research material obtained in the form of specimens, records, or data and an indication of whether the material will be obtained specifically for research.

8. *Statistics*: Provides a description of the statistical analysis to be used. Include the number of subjects per treatment group and the rationale for the population sample size. Identifies the level of statistical significance to be used.
9. *Recruitment of Subjects*: A description of the plans for the recruitment of subjects, consent procedures, who will obtain the informed consent, the nature of the information to be provided and how it will be documented.
10. *Potential Risks*: A description of any potential risks or discomforts for the subjects and the description of the methods of assessing and analyzing risk parameters.
11. *Special Precautions*: Description of procedures for protecting against any potential risks and the ensuring of necessary medical intervention in the event of adverse effects to the subjects.
12. *Procedures to Maintain Confidentiality*: Discusses how the confidentiality of participating subjects will be maintained and what information about an individual research subject would be disclosed.
13. *Potential Benefits*: Describes the potential benefits of a study and the methods for determining efficacy of treatment.
14. *Risk/Benefit assessment*: Discusses why the risks to subjects are reasonable in relation to the benefits anticipated from the study.

Following the GCP guidelines in conducting clinical trials is a requirement of industry-sponsored investigations. The utilization of these guidelines in all human investigation of drugs and devices is best practice. Everyone on the clinical research team who is involved in obtaining data, consent, records management and analysis should be familiar with the guidelines and create standard operating procedures (SOPs) in line with them. These SOPs and a thorough understanding of the GCP principles and guidelines form the foundation for protecting the human subject and the conduct of sound clinical investigation.

Designing Clinical Research

The value of research depends on the integrity of its study results. One of the ethical justifications for research involving human subjects is the social value of advancing scientific understanding and promoting human welfare by improving healthcare. But if a research study is so flawed that little or no reliable information will result, it is unethical to put the subjects at risk. Therefore, careful planning of the research design is paramount to a successful clinical trial project.

Fifteen steps outline a basic method in designing and performing a research project. The first nine steps (Table 1) must be accomplished even before data collection begins; while the last six (Table 2) are the final steps carried out in data collection, analysis and publishing phase. This section will briefly summarize those 15 steps.

The researcher must realistically assess the main idea and narrow its scope to something that can be accomplished with time and the resources readily available. Early in the planning process, the researcher must develop and prioritize all objectives that are

TABLE 1

1. Formulate sound ideas to research.
2. Develop and prioritize objectives.
3. Define study population.
4. Refine objectives into testable hypotheses.
5. Anticipate error and bias.
6. Develop study design.

to be met through the research. This is crucial in that some of the objectives will compete for study resources, finances and personnel time. Prioritizing these objectives will alleviate further dilemmas in the future. In defining the study population, the researcher should pose the question “What is the group of people to which the study’s results are to be generalized at the end of the study?”. A decision must be made whether to enroll the whole target population or to select a smaller sample from that population. Once the objectives have been written and study population determined, the objectives have to be refined into a written testable hypothesis. Additionally, the way the hypothesis is expressed has important implications for how the study is actually designed. This is why the

hypothesis must be quantitatively stated before the study design can be determined. Another set of issues that must be considered is that results of the study may be subject to error or bias. To minimize the occurrence of error and bias, it is vital to anticipate beforehand the possibility of the types of error that might occur.

After meeting the issues raised in the initial 5 steps, constructing the study design will identify the actual purpose of the study. Study designs can be divided into two major types: experimental and observational. Experimental Designs are experiments where the treatment or risk factor is assigned by the investigator. Usually the assignment is randomly determined using a system of random numbers; ideally both the investigator and subject are unaware of which groups the subjects were assigned to (the so-called ‘double-blind’ design). Observational Study Designs indicates that the determination of

who receives the treatment or risk factor is independent of the investigator. Instead, investigators act upon statistical analyses to obtain a causal inference possible from the experience. In addition, another important component of this design is determining the sample size needed. If too few subjects are chosen, the study is likely to experience a sampling error; too many subjects may increase the cost of the study beyond the budgeted financial resources. In some instances, consulting a biostatistician may lessen the guesswork in estimating the required sample size, since the best method of estimation depends on the type of study design selected. The research protocol enumerates the mechanics of the proposed research study. By writing this, the investigator clarifies the exact intent and details of the research plan. Collaboration with other investigators is helpful to filter out issues that may spark disagreements; it is better to “straighten out” these issues early in the design phase than after the data is collected.

The next steps deal with managing data collection and ensuring that utmost accuracy is observed during this process. As stated earlier, the validity of the research is only as good as the data extracted from it. The investigator should undertake measures to ascertain that the data collected is, in fact, compliant and consistent with the proposed research design. Validity tests can be established to meet these requirements. Monitoring the actual data collection may increase the probability that data is reliable. All these quantitative records are managed through a database. Whether they are computer-based or inscribed manually, data keeping represent yet another important component regarding research documentation. It is a wise procedure, however, to keep data sets fully documented in a notebook and use a computer program to query and manipulate the data. Although this procedure seems redundant, it rewards itself later in the analysis phase when the many complex features of the collection phase begin to fade through time. Often, simply keeping a notebook to file vital pieces of documentation saves confusion later in the study.

While some investigators can get preoccupied with statistical tests of significance, the real heart of data analysis lies in conveying data and testing the hypothesis through tables, charts and graphs. Ideally, the type of charts or graphs can be dependent upon the type of data being presented. It is important that the investigator anticipate the statistical test that is to be applied with the results. To choose the right test, the investigator may consider working closely with a statistician to ensure that the analyses are done correctly. After the main hypothesis test is performed, the investigator and/or the statistician will generally perform additional analyses to elaborate on the findings.

TABLE 2

10. Manage and monitor data collection.
11. Manage the database.
12. Analyze results into tables & graphs.
13. Test the hypothesis with correct statistical test.

These additional analyses should be anticipated in the design phase so that variables will be appropriately determined and the sample sizes will be adequate for them. Finally, the end product of a successful study is the publication in a scientific journal. One should decide on a scientific journal before writing the article. A good scientific article presents no more than four or five main points that are the important findings of the results section. After an initial draft is made, it should be revised repeatedly and passed among colleagues for review and revision.

Most scientific papers now have multiple authors. It is important early on that the researchers determine the order in which the authors are to be listed. Usually, the first author to be listed is the individual who actually performed the majority of the experiment and brought the study to completion. The other authors are collaborators who perform specific tests to aid in the completion of the study. The order of their names is ranked according to the relative importance of their contributions.

Designing clinical research projects is a meticulous yet rewarding process that requires attention to a large number of details that each of which can influence the success or failure of a project. The investigator must be fully aware of the many aspects that must be carefully planned even before the first step is carried out.

Research Misconduct/Conflict of Interest

Research misconduct and conflict of interest are detrimental to the scientific objectivity where they raise doubts about the integrity of the scientific enterprise and to the extent to which we can trust the work of others. Making up data or results (fabrication), changing or misreporting data or results (falsification), and using the ideas and words of another person without giving appropriate credit (plagiarism)—all strike at the center of the values on the foundation science is based. These acts of scientific misconduct not only hinder scientific progress but the entire set of values on which the scientific enterprise rests. The consequences resulting from this misconduct are extreme: it can harm the individuals outside of science (when falsified results become the standard in medical treatment); it squanders public funds and attracts the attention of those who criticize science. As a result federal agencies may get involved. In addition to falsification, fabrication and plagiarism, other ethical misbehavior directly associated with research can cause serious harm to both individuals and institutions. Instances include cover-ups of misconduct in science, malicious allegations of misconduct in science and violations of due process in handling complaints of misconduct in science.

The traditional source of the regulation of scientific conduct has been the scientific community itself; regulations adopted by the National Science Foundation and the Public Health Service define misconduct to include “other serious deviations from accepted research practices”, leaving open the possibility that other actions could be considered misconduct in science. Such regulation has its limits, however, and various legal regulations have emerged. Some of the mechanisms to ensure *responsible* and *respectable* science are legalistic procedures and documentation, but some are more values or principles in which the credible scientific enterprise must adhere. Examples of these mechanisms are peer review, academic and editorial freedom; the obtaining and signing of consent forms; academic structure and mentoring relationships; and most importantly the IRBs, who oversee and advise researchers of overall scientific credibility of the project. *Responsible* science is one that is cognizant of its appropriate applications and misapplications, whereas *respectable* science has to do with securing credible, high quality scientific knowledge. Take into account the manipulation or fabrication of scientific data. Such a deceptive act is exploitation of all research subjects who have participated in the research, under a promise of noble scientific enterprise. Additionally, altering research data deliberates the progress of science, undercuts the social value of science, and perhaps damages the collective network of knowledge generated by science.

Conflict of Interest

There are times when professional judgement is unduly influenced by external factors. Ultimately this judgement that concerns a primary interest (such as a patient's welfare or the validity of research) tends to be influenced by a secondary interest, such as financial gain. For instance, a researcher may have a financial interest (or has stock) in a certain pharmaceutical company that might create a bias in scientific decisions concerning a research project. Or a scientist might receive a manuscript or proposal to a review that discuss work similar to but a step ahead of that being done by the reviewer. This conflict of interest is nearly universal, from physicians accepting fees for patient care to academic promotion requiring scientific publications. A conflict of loyalty may also occur between the welfare of the patient and the quality of the research project. Conflicts of loyalty have to do with the fidelity to particular duties in relationships with people, whereas conflicts of interest have to do usually with conflict between selfish interests of, in this case, the researcher over or against the interest of the patient or a larger organization.

Openness about potential conflicts of interest is essential as there is increasing evidence that suggests that biomedical-industry financial support for universities and faculty investigators influence either the design of clinical trials, the gathering of data in those trials, or the reporting of trial results. The industry's ever increasing financial relationships with universities and individual investigators attract the attention of the public whether the university or the investigators can achieve financial or personal gain without sacrificing scientific integrity in some way. With this continued industry support comes the substantial risk of harm created by conflicts of interest—risks to the public's trust in its physicians, and the risk to trust investigators in reported research results.

Investigator relationships with the biomedical industry range from the trivial to the financially rewarding including minor gifts, honoraria for speaking engagements, consulting agreements, royalties for licenses or patent technologies and equity in a company. Similarly, investigator activities that could be influenced include inappropriate use of institutional assets or resources for personal gain, disclosing confidential or proprietary information for personal gain, and the conduct of research through either sponsored research agreements or clinical trial agreements. Whether gifts or honoraria create potential conflicts of interest depends on the size of the gifts, how frequently they are given (and received), and the context in which the gifts are exchanged. The point about gifts given by the industry is that they are designed to create a relationship between the giver (the company) and the investigator-recipient so as to influence the recipient's behavior in favor of the company. Investigators need to be cognizant of how receiving gifts can greatly influence his activities. To address these situations, the investigator should determine if guidelines, policies, or standards of conduct are in place which may be consulted; the investigator should gather and analyze the situation if there is potential conflict of interest; if there is a possible conflict, the investigator must disclose the facts regarding the situation to the appropriate entity. By taking these steps, the investigator can properly manage potential conflicts of interest events should they arise.

PROFICIENCY TEST

PROFICIENCY TEST

1. Revelation of researcher misconduct in the Tuskegee Syphilis study led in part to publication of 45 CFR 46, a regulation which governs the review and performance of clinical research.
TRUE or FALSE
2. The Belmont Report outlined the ethical principles that serve as the moral foundation for our system of human research protection.
TRUE or FALSE
3. Nazi atrocities in World War II drew attention to the lack of international standards in research and led to the formulation of the Nuremberg Code.
TRUE or FALSE
4. The Belmont Report established 3 basic ethical principles—respect for persons, justice, and balance—which are the cornerstones of research regulations.
TRUE or FALSE
5. The Informed Consent directly reflects the principle of balance.
TRUE or FALSE
6. A patient who has provided informed consent is one who has voluntarily agreed to participate in research.
TRUE or FALSE
7. The Informed Consent should be as detailed as possible and works best when written at the 12th grade reading level.
TRUE or FALSE
8. Non-English speaking participants never need a consent form written in their native tongue in order to provide informed consent.
TRUE or FALSE
9. An informed consent should not ask a research subject to waive any legal rights.
TRUE or FALSE
10. The Informed Consent is a single event, ending when the individual signs the form.
TRUE or FALSE
11. The Declaration of Helsinki was the beginning of the review mechanism that is now fundamental to our current system of human subject protection—the IRB.
TRUE or FALSE
12. IRB membership must be diverse and sensitive to community standards.
TRUE or FALSE

13. Essentially, an IRB reviews research and ensures that the rights and welfare of human subjects are protected. **TRUE or FALSE**
14. Women should never be included in a research study because of possible pregnancy and the need to avoid unnecessary risk to a fetus. **TRUE or FALSE**
15. Federal regulations require that special considerations be employed in research involving vulnerable populations. **TRUE or FALSE**
16. The Declaration of Helsinki is the basis of the Good Clinical Practice standard developed by the International Conference on Harmonization. **TRUE or FALSE**
17. The Good Clinical Practice standard only applies to clinical trials involving drugs, not to device trials. **TRUE or FALSE**
18. If performing research under the Good Clinical Practice standard, IRB review and approval is not needed. **TRUE or FALSE**
19. There is no requirement that informed consent be obtained as part of a Good Clinical Practice research study. **TRUE or FALSE**
20. The utilization of Good Clinical Practice standards in clinical research is considered good practice. **TRUE or FALSE**
21. When designing a clinical research project, one must give consideration to the fact that the value of the research depends on the integrity of the study results. **TRUE or FALSE**
22. An experimental research study is one which a double-blind design would be utilized. **TRUE or FALSE**
23. When writing a scientific paper, the order in which the names of the authors are listed should be dependent solely on seniority. **TRUE or FALSE**
24. Research misconduct includes such actions as fabrication of data, plagiarism, and falsification of results. **TRUE or FALSE**
25. A researcher who is a major stockholder in a pharmaceutical company may have a conflict of interest if performing a clinical study on a new drug produced by that company. **TRUE or FALSE**

North Texas Institutional Review Board General Workflow

