Informed consent form of subjects

Study name：EFFECT-neo: A Prospective, Open-label, Multicenter Phase III Study to Evaluate Efficacy and Safety of Pembrolizumab Combined With Standard Chemotherapy vs. Standard Chemotherapy Given Prior to Surgery for stage IIIA- IVB Locally Advanced Head and Neck Squamous Cell Carcinoma

Research institute：Beijing Tongren Hospital

Dear patient:

We are about to conduct a clinical study and you may be eligible for this study, so we invite you to take part in this study. This informed consent will introduce you to the purpose, process, benefits, risks, etc. of this study. Please read it carefully and make a careful decision whether to participate in the study.

When the researcher is explaining the content of this informed consent form to you, you can ask questions at any time and let him/her explain to you what you do not understand. You can make a decision after discussing it with family, friends, and your treating doctor.

The project leader of this study is Zhigang Huang from Beijing Tongren Hospital Affiliated to Capital Medical University.

Research Funding Source: Self-selected topics.

1. Why is this research conducted?

Head and neck squamous cell carcinoma (HNSCC) refers to a series of tumors

in the head and neck region, including the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid and salivary glands. Malignant tumors of the head and neck account for about 19.9% to 30.2% of all tumors in the body, and the incidence rate ranks sixth among all malignant tumors. More than 90% of the pathological types are squamous cell carcinomas [1-2]. The treatment of squamous cell carcinoma of the head and neck is mainly based on surgery. Early cases can be cured by simple surgical resection or radiotherapy, and advanced cases can be cured by surgery combined with radiotherapy or chemotherapy, which can achieve better curative effect. However, most patients with head and neck tumors are already in locally advanced (stage III-IVB) or advanced stage when they see a doctor, and may have lost the opportunity for surgery, so they can only choose comprehensive treatment based on radiotherapy and chemotherapy.

Neoadjuvant chemotherapy, also known as induction chemotherapy, refers to chemotherapy used before surgery or radiotherapy. It has good patient compliance, can reduce tumor burden, improve the rate of organ function preservation in surgical patients, eliminate potential metastatic lesions, and reduce distant metastasis. risks and other advantages [3]. Clinical research on induction chemotherapy began in the mid-1970s, and the most commonly used induction chemotherapy regimen was PF regimen (cisplatin (cisplatin, P) + 5-fluorouracil (5-fluorouracil, 5-FU). Along with paclitaxel (docetaxel, T), and is

also exploring whether paclitaxel can be added to the induction chemotherapy regimen. For resectable HNSCC, the European GORTEC study showed that the addition of paclitaxel (T) on the basis of the PF regimen can improve the efficacy of induction chemotherapy, and its pCR rate The rate reached 13.4%, and the ORR was as high as 80%. A number of Phase II and Phase III clinical studies concluded that induction chemotherapy can reduce the rate of distant metastasis[4-6].

PD-L1 is a key negative regulator of autoreactive T cells, and plays a role in maintaining peripheral immune tolerance and suppressing autoimmunity in multiple ways, promoting T cell exhaustion and dysfunction, and tumor cells evading immune surveillance. PD-1/PD-L1 monoclonal antibody restores the function of tumor-specific T cells by blocking the combination of PD-1 and PD-L1, and achieves the effect of enhancing anti-tumor immunity. It has been used to treat a variety of tumors. Pembrolizumab is a fully humanized IgG4-kappa anti-PD-1 monoclonal antibody. The FDA approved pembrolizumab in 2016 for the treatment of platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma. Currently, pembrolizumab combined with chemotherapy can be used as the first-line treatment for recurrent/metastatic head and neck squamous cell carcinoma. At the same time, pembrolizumab can also be used as a second-line treatment for recurrent/metastatic head and neck squamous cell carcinoma that is resistant

to beneficiation.

The efficacy of PD-1 monoclonal antibody as a neoadjuvant therapy in head and neck squamous cell carcinoma is not yet clear, but in view of the good effect of immunotherapy in head and neck squamous cell carcinoma, induction therapy with PD-1 monoclonal antibody is considered to have a good clinical effect Application prospects [7]. At present, relevant clinical trials are underway, such as a phase III clinical trial KEYNOTE-689 (NCT03765918) for cancers of the oral cavity, oropharynx, hypopharynx, and larynx, using pembrolizumab as neoadjuvant therapy, compared with traditional surgery combined with adjuvant therapy program, and the results of the study are yet to be published. The 2020 ASCO meeting reported the study of neoadjuvant therapy nivolumab combined with carboplatin and paclitaxel for resectable locally advanced head and neck cancer. The surgery rate was 100%, CT showed no tumor progression, and the margin negative rate was 100%. , The pathological complete response rate (pCR) was 42%. Grade 3 toxicity occurred in 37% of patients, and grade 3-4 neutropenia occurred in 4 patients. It suggested that the neoadjuvant therapy of nivolumab combined with carboplatin and paclitaxel was well tolerated and the efficacy was satisfactory[7].

In summary, we speculate that, compared with the traditional TPF induction chemotherapy regimen, the induction chemotherapy regimen of pembrolizumab combined with cisplatin and nab-paclitaxel may be safer and

more effective, and easier for clinical application. At present, there are no research reports on the induction chemotherapy of pembrolizumab combined with cisplatin and nab-paclitaxel for patients with locally advanced operable head and neck squamous cell carcinoma. We intend to conduct a randomized controlled study on the efficacy and safety of pembrolizumab combined with chemotherapy as neoadjuvant therapy in Chinese patients with operable head and neck squamous cell carcinoma, and provide a basis for the neoadjuvant therapy of pembrolizumab combined with chemotherapy.

Objective: To conduct a randomized controlled study on the efficacy and safety of neoadjuvant pembrolizumab combined with standard chemotherapy in Chinese patients with resectable head and neck squamous cell carcinoma. To evaluate the primary lesion pathological complete response rate (pCR) of pembrolizumab combined with standard chemotherapy neoadjuvant therapy in patients with locally advanced head and neck squamous cell carcinoma.

1. Who will be invited to participate in this study?

Inclusion criteria

1) Patients with untreated stage IIIA-IVB head and neck squamous cell carcinoma (including oral cavity cancer, oropharyngeal cancer, hypopharyngeal cancer, laryngeal cancer) diagnosed by histology and/or cytology
2) Patients with non-distant metastases

3) The researchers believe that they can safely receive pembrolizumab combined with standard chemotherapy, or neoadjuvant chemotherapy with standard chemotherapy
4) Age 18-75 years old
5) ECOG 0-1
6) Measurable disease as defined by RECIST v1.1
7) Organ function is normal
8) Female and male participants of reproductive potential must agree to use appropriate contraception throughout the study period and for 180 days after the last study treatment
9) Male participants must refrain from donating sperm for the entire duration of the study and for 180 days after the last study treatment.

Exclusion Criteria:

1) There is distant metastasis
2) Tumors outside the oropharynx, larynx and hypopharynx or oral cavity within 2 years, such as nasopharynx, sinus, other paranasal, esophageal cancer or other unknown or unknown primary head and neck cancer
3) Female subjects with a positive urine pregnancy test (with or without cisplatin) within 72 hours before the start of the study or within 24 hours after starting radiotherapy
4) Received a live vaccine within 30 days before enrollment

5) Diagnosed with immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before enrollment
6) In the past 3 years, there are other malignancies known to be progressing or requiring active treatment, except basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (such as cervical carcinoma in situ or breast cancer)
7) Have radiologically detectable (even if asymptomatic and/or previously treated) central nervous system metastases and/or carcinomatous meningitis
8) Have undergone surgery before starting the study or have not fully recovered from toxicity or complications caused by the intervention;
9) Have had allogeneic tissue/solid organ transplantation
10) Severe hypersensitivity to pembrolizumab or any of its adjuvants, radiotherapy, platinum, paclitaxel, 5-FU or its analogs (≥3 grade)
11) Suffering from active autoimmune disease, requiring systemic treatment in the past 2 years
12) Have a history of (non-infectious) pneumonia requiring steroid therapy
13) Suffering from active infection within 1 month, requiring systemic treatment
14) History of human immunodeficiency virus (HIV) infection

15) Have a history of hepatitis B or are positive for hepatitis B virus (defined as a positive reaction to hepatitis B surface antigen [HBsAg]) or active hepatitis C (defined as detection of hepatitis C virus [HCV] ribonucleic acid)

16) Have any medical history, treatment or laboratory abnormalities that may confound the study results, interfere with the participant's participation throughout the study period, or be detrimental to the participant's best interests

17) Have a known history of psychiatric or substance use disorder

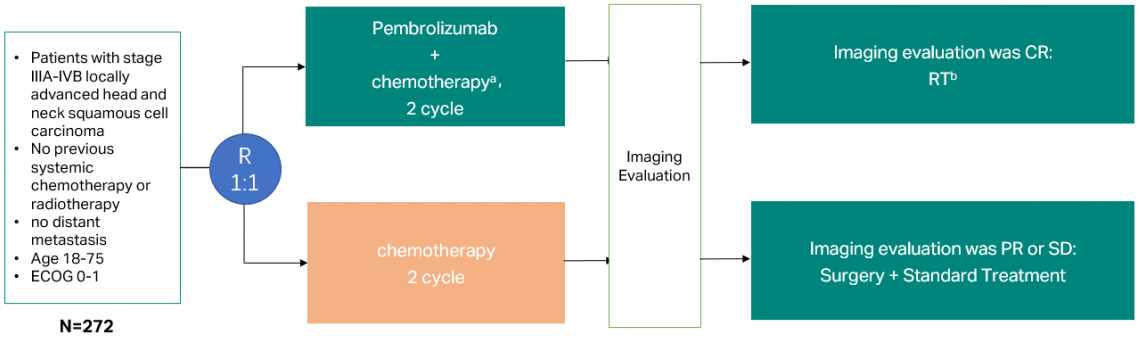
The study plans to enroll 272 subjects

2. How was this research conducted?

Patients who meet the inclusion criteria are randomized 1:1, and given pembrolizumab 200 mg d1+ chemotherapy (see 3.1 for detailed chemotherapy regimen) for 2 cycles (experimental group), 2 cycles of chemotherapy (control group), and then stratified according to the patient's condition. If the imaging evaluation after neoadjuvant treatment is CR, adjuvant radiotherapy (60-66Gy) will be given; if the imaging evaluation is PR or SD, surgery (within 2 weeks) will be performed, followed by standard treatment. If the imaging evaluation is PD, the patients will be removed from the group and given standard treatment.

Neoadjuvant therapy, also known as induction therapy, refers to systemic therapy such as chemotherapy/targeting/immunization used before surgery or radiation therapy. It has good patient compliance, can reduce tumor burden,

improve radiotherapy sensitivity, and improve the survival rate of surgical patients. The preservation rate of organ function, the elimination of potential metastatic lesions, and the reduction of the risk of distant metastasis, etc.



Note: If the imaging evaluation is PD, then withdraw from the study and receive standard treatment

Primary endpoint: pCR

Secondary endpoints: 1y/2y-EFS, throat Protection rate, 2y-OS, safety, etc.

a. Chemotherapy drugs include: cisplatin, carboplatin, nedaplatin, paclitaxel liposome, nab-paclitaxel, docetaxel, fluorouracil
b. Histopathology of the primary tumor must be taken before radiotherapy.
c. EFS is defined as the time from randomization to any event, including disease progression, discontinuation of treatment for any reason, or death

Enrolled patients need to complete the preoperative examination (blood routine, blood type, urine sediment, coagulation function, biochemical comprehensive items, immunity, electrocardiogram, neck CT/MRI, cervical lymph node ultrasound, stroboscope) if found preoperative If the examination is abnormal, it is necessary to complete relevant specialist examinations to rule out the risk of comprehensive surgery. Postoperative follow-up follow-up on time review. Enrollment in this study will not add additional tests and inspection items.

During the study period, the adverse reactions of patients will be closely monitored, and the time, grading, treatment measures, and outcomes will be recorded. All patients will be re-examined every 3 months for 1 year; after 1 year, they will be re-examined every 6 months for 3 years; relapse and survival data of patients will be recorded。

3. What are your possible benefits from participating in this research?

There is no obvious benefit prediction, and the two groups of patients may have the same prognostic benefit. So take part in this study and we hope that the information you get from your participation in this study will benefit patients with the same condition as you in the future.

In addition, accepting tumor tissue biomarker examination may not directly benefit you, but your participation will contribute to further medical research and understanding of such diseases, and improve the diagnosis and treatment of diseases in the future. Here, we thank you for your participation in scientific research and your contribution to the development of medicine!

4. What are the possible risks and inconveniences for you to participate in this study?

The use of immunological drugs, chemotherapy drugs, radiotherapy, and surgical methods were carried out in full accordance with the norms. There are corresponding complications in the use of drugs, please refer to the introduction of drug instructions for details. Surgery still has surgery-related risks, so it may affect intraoperative bleeding, nerve damage, and postoperative complications. For details, refer to the content of informed consent for surgical risks.

Attachment: Possible Risks of Study Drug Therapy

Pembrolizumab AE management

1. Immune-related pneumonia:

Among patients receiving pembrolizumab, a total of 278 (4.4%) patients

developed pneumonia, 122 (1.9%), 70 (1.1%), and 15 grade 2, 3, 4, and 5 cases, respectively. (0.2%) and 12 cases (0.2%), the median time to the onset of pneumonia was 3.2 months (range 2 days to 26.8 months), and the median duration was 2.0 months (range 1 day to 25.34 months) . Patients with a history of previous chest radiation had a higher incidence of pneumonia (8.1%) than those without prior chest radiation (3.3%). Pneumonia led to discontinuation of pembrolizumab in 105 (1.7%) patients. 151 patients recovered from pneumonia, and 2 patients recovered with sequelae. Among patients with non-small cell lung cancer, a total of 160 patients (5.7%) developed pneumonia, 62 cases (2.2%), 47 cases (1.7%), and 14 cases (0.5%) of grade 2, 3, 4, and 5 pneumonia respectively and 10 cases (0.4%) in NSCLC patients with previous thoracic radiotherapy, the incidence of pneumonia was 8.9%.

2. Immune-related colitis:

Among patients receiving pembrolizumab, colitis occurred in 115 patients (1.8%), with 33 (0.5%), 66 (1.0%), and 4 (1.0%) grade 2, 3, and 4 cases, respectively. 0.1%), the median time to onset of colitis was 4.3 months (range 7 days to 24.3 months), the median duration was 0.9 months (range 1 day to 10.5+ months), and colitis resulted in 31 cases (0.5%) patients discontinued pembrolizumab treatment. Eighty-nine patients recovered from colitis, and 2 patients had sequelae after recovery.

3. Immune-related hepatitis:

Hepatitis occurred in 57 (0.9%) patients receiving pembrolizumab, with 9 (0.1%), 36 (0.6%), and 9 (0.1%) grade 2, 3, and 4 cases, respectively. %), the median time to hepatitis onset was 2.8 months (range 8 days to 21.4 months), the median duration was 1.1 months (range 1 day to 20.9+ months), and hepatitis

resulted in 24 cases (0.4%) patients discontinued pembrolizumab treatment. 39 cases of hepatitis were cured.

4. Immune-related nephritis:

Among patients receiving pembrolizumab monotherapy, a total of 25 patients (0.3%) developed nephritis, 8 patients (0.1%), 14 patients (0.2%) and 1 patient (<0.1%). The median time to onset of nephritis was 3.5 months (range 12 days to 21.4 months). Median duration was 1.9 months (range 6 days to >12 months). Nephritis led to discontinuation of pembrolizumab in 10 (0.2%) patients. 15 patients recovered from nephritis, and 3 patients recovered with sequelae. In patients with non-squamous NSCLC treated with pembrolizumab plus pemetrexed lead chemotherapy (Cn=488), the incidence of nephritis (all grades) was 1.4%, and the incidence of grade 3 nephritis was 0.8%, The incidence of grade 4 nephritis was 0.4%.

5. Immune-related endocrine diseases:

A total of 47 (0.7%) patients receiving pembrolizumab developed adrenal insufficiency, including 20 (0.3%), 20 (0.3%), and 3 patients with grade 2, 3, or 4 (<0.1%). The median time to onset of adrenal insufficiency was 5.4 months (1 day to 17.7 months). Median duration was not reached (3 days to over 26.2 months). Four patients (0.1%) discontinued the drug due to adrenal insufficiency. Sixteen patients with adrenal insufficiency were cured, and 4 patients were cured with sequelae.

Among the patients treated with pembrolizumab, a total of 39 patients (0.6%) developed hypophysitis, with 14 (0.2%), 21 (0.3%), and 1 (0.3%) grade 2, 3, and 4 cases (<0.1%). The median time to onset of hypophysitis was 5.6 months (range 1 day to 17.7 months). Median duration was 3.3 months (range 3 days to

20+ months). Hypophysitis led to discontinuation of pembrolizumab in 8 (0.1%) patients. Eighteen patients recovered from hypophysitis, and 9 patients recovered with sequelae.

Hyperthyroidism occurred in a total of 263 (4.1%) patients receiving pembrolizumab, with 68 (1.1%) and 7 (0.1%) grade 2 or 3 cases, respectively. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 23.2 months). Median duration was 1.9 months (range 4 days to 29.2+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 3 (<0.1%) patients. 207 patients (78.7%) were cured of hyperthyroidism, and 5 patients were cured with sequelae.

Hypothyroidism occurred in a total of 696 (11.0%) patients receiving pembrolizumab, with 513 (8.1%) and 8 (0.1%) grade 2 or 3 cases, respectively. The median time to onset of hypothyroidism was 3.4 months (range 1 day to 20.5 months). Median duration was not reached (range 2 days to 32.6+ months). Two patients (<0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism was cured in 159 patients (22.8%), and 10 patients were cured with sequelae. Among 909 HNSCC patients treated with pembrolizumab monotherapy, hypothyroidism occurred in 16.1% (all grades) and grade 3 in 0.3%. Among 276 HNSCC patients treated with pembrolizumab combined with platinum and 5-FU chemotherapy, the incidence of hypothyroidism was 15.2%, all grade 1 or 2.

6. Immune-related and adverse reactions:

Among patients receiving pembrolizumab, a total of 93 (1.5%) patients experienced immune-related severe skin reactions, with 12 (0.2%) and 67 (1.1%) grade 2, 3, or 5 cases, respectively. %) and 1 case (<0.1%). The median

time to onset of severe skin reactions was 3.2 months (range 3 days to 19.4 months). Median duration was 1.8 months (range 1 day to 27.3+ months). Severe skin reactions led to discontinuation of pembrolizumab in 9 (0.1%) patients. 67 cases of severe skin reactions were cured.

Treatment adjustments for pembrolizumab-related immune-related AEs

Dosing suspension or discontinuation may be required based on individual patient safety and tolerability. No dose increase or decrease is recommended

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5. How does your participation in this research affect your daily life?

When you decide whether to participate in this study, please carefully consider the possible impact of the check-ups and follow-ups listed above on your daily work, family life, etc. Consider time and traffic issues for each postoperative review. If you have any questions about the inspections and steps involved in the test, you can consult us.

If the investigator believes that a certain drug treatment is necessary for the subject's health and is not expected to interfere with the evaluation of this study or cause drug interactions, it can continue to be used during the study.

This study requires contraception for the subjects, and female and male participants of reproductive potential must agree to use appropriate contraception throughout the study and for 180 days after the last study treatment.

6. If you do not participate in this study, are there any other treatment options?

When you decide not to participate in this study, it will not affect the standard treatment of your disease. Treatment methods will be rationalized and individualized in accordance with guidelines and other standards, including surgical treatment, radiotherapy and chemotherapy, targeted therapy, etc. The treatment plan will be formulated on the basis of follow-up examination and judgment.

7. Who will pay for your participation in this study?

Because this study will not perform any additional examinations and test items on the patients, postoperative follow-up follow-up will be in accordance with relevant diagnostic and treatment norms.

The cost of chemotherapy, radiotherapy and surgery involved in the study shall be borne by the patients themselves according to the standard treatment charges. (The pembrolizumab involved in immunotherapy is purchased by the patient at his or her own expense throughout the course of the treatment, and the charity drug donation policy is as follows: purchase 2 cycles plus 2 cycles, and after purchasing 2 cycles, donate the drug to 15 cycles.)

8. Will you be compensated for participating in this research study?

Subjects participating in the study will not be compensated if there is no accidental injury in the routine inspection, detection and treatment completed as planned during the trial period.

9. What if you have a research-related injury?

When your health is harmed by participating in this study, please inform the researcher (contact person and contact number), and we will take necessary medical measures. According to the relevant laws and regulations of our country, when research-related injuries occur, the research institution of this research will bear the corresponding medical expenses and provide corresponding economic compensation. *

This study provides clinical trial group insurance for the enrolled personnel. Please refer to the appendix for specific insurance related content.

Note: With reference to Article 43 of my country's drug clinical trial management regulations, the sponsor is required to bear the medical expenses and provide compensation when research-related injuries occur. When this research is not funded by the industry, it is necessary to explain the treatment and compensation measures taken in the event of research-related injuries.

10. Under what circumstances may the study be terminated early?

Events that may lead to early termination of the trial or closure of the trial site include, but are not limited to: new drug toxicity results, trial benefit and follow-up completion for subjects, non-adherence to the trial protocol, changes in the study drug development plan, subject recruitment Progress is slow or data quality is poor. Once there is any information that may affect your decision whether to continue participating in this study, we will promptly inform you.

The sponsor or regulatory agency may also terminate the study during the study period. In the event of early termination of the study, we will notify you in time, and your study doctor will provide advice on your next treatment plan based on your health status.

For subjects who drop out halfway, we have a final follow-up plan for safety reasons, and you have the right to refuse. In addition, if we discover new information related to your health and rights after you log out, we may contact you again.

After the subject withdraws, it needs to be clear that no new data related to it will be collected in the future. And make detailed instructions to the subjects on how to deal with the research data collected before and the data withdrawn due to adverse reactions.

In principle, after you withdraw, the researcher will keep your relevant information strictly until it is finally destroyed, and will not continue to use or disclose such information during this period. However, in the following rare cases, the researcher will continue to use or disclose your relevant information, even if you have withdrawn from the study or the study has ended. These situations include:

- Removal of your information will affect the scientific nature of the research results or the evaluation of data security;

- Provide some limited information for research, teaching or other activities (this information will not include your name, ID number, or other personal information that can identify you);

When government regulators need to oversee a study, they will ask to see all

study information, including information about your participation in the study at the time.

11. Do you have to participate in and complete this study?

Your participation in this study is completely voluntary, you can refuse to participate, and you also have the right to withdraw at any stage of the study without discrimination or retaliation, and your medical treatment and rights will not be affected.

We will keep you informed during the study of any new information that may affect your decision to continue participating in the study.

12. Will your personal information be kept confidential?

If you decide to participate in this research study, your participation in the study and your personal data during the study will be kept confidential. Your tissue and blood samples will be identified with a study number number rather than your name. Information by which you can be identified will not be disclosed to members outside the research team without your permission. All study members and study sponsors are required to keep your identity confidential. Your file will be kept in a locked filing cabinet and will only be accessible to researchers. In order to ensure that the research is carried out in accordance with the regulations, when necessary, members of the government management department or the ethics committee can check your personal data in the research unit according to the regulations. When the results of this study are published, no personal information about you will be disclosed. You have the right to consent/authorize at any time after your participation in the

study; the right to refuse to sign the consent/authorization form.

13. Who can I contact if I have questions or difficulties?

If you have any questions related to this study, or if any injury related to this study occurs, please contact (researcher) Zhang Yang at 13311365369.

If you have questions related to your own rights and interests, you can contact the Ethics Committee of Beijing Tongren Hospital Affiliated to Capital Medical University at 010-58268486 ext. 8004.

Signature Page of Informed Consent

Subject declaration

I am aware of the purpose, process, risks and benefits of this study.

I have had ample time and opportunity to ask questions, and my questions have been answered satisfactorily.

I am aware of whom to contact with questions, concerns, suggestions, or further information about this study.

I have read this informed consent form carefully and agree to participate in this study.

I understand that I can withdraw from this study at any time during the study without any reason.

I will be given a copy of this informed consent form with my signature and that of the researcher.

Subject signature	Date
Legal guardian's signature (If necessary, please indicate the relationship with the subject)	Date
Impartial Witness Signature (If necessary)	Date

Researcher statement

"I have informed the subject of the purpose, process, risks, and benefits of the study, given the subject enough time to read this informed consent form or discuss it with others, and answered questions about the study in detail; I have Informed the subject of contact information for research-related questions; I have informed the subject that they may withdraw from the study at any time; I have informed the subject that they will be given a copy of this informed /her signature."

Signature of the researcher who obtained the informed consent	Date
phone number	