INSTITUTIONAL ETHICS COMMITTEE
(Reg. No. – ECR/287/Inst/WB/2013/RR-19)
MEDICAL COLLEGE, KOLKATA
88, COLLEGE STREET, KOLKATA 700073, WEST BENGAL, INDIA

Ref No. MC/KOL/IEC/NON-SPON/1675/11/2022 dated 30/11/2022

To,
Dr. Swadha Pandey,
1st Year Junior Resident,
Dept. of Gynaecology & Obstetrics,
Medical College, Kolkata

Sub: IEC-MCH Decision of the review of study protocol.

Study Title: LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS

Dear, Swadha Pandey,

In the meeting held on 10th December 2022 in College Council room at Medical College, Kolkata, the members of the IEC, Medical College, Kolkata, reviewed and discussed your synopsis to conduct the study as proposed.

The following members of the committee were present:

Chairperson: Prof. Nandita Basu, Ex-Director, School of Tropical Medicine & Chair Person, IEC, MCH, Kol.
Member Secretary: Prof. Debasis Das, Prof. & Head, Dept. of Community Medicine, MCH, Kolkata

Members:

1. Prof. Dipak Kumar Sarkar, Prof. & Head, Dept of Pharmacology, MCH, Kolkata
2. Prof. Aniruddha Sengupta, Prof. & Head, Dept. of Orthopedics, Medical College, Kolkata
3. Dr. Raja Bhattacharya, Associate Prof., Dept. of General Medicine, Member (Clinician), IEC ,MC, Kolkata.
4. Dr. Bhawna Bhutoria Jain, Professor, Dept. of Pathology, Govt. Medical College, Rampurhat, Member(Basic Scientist), IEC, MC, Kolkata.
5. Dr. Sebanti Bhattacharyya, Associate Professor & Officer-In-Charge, Sister Nibedita Government General Degree College for Girls
6. Mr. Hironlal Majumder, Legal Expert
7. Sri. Ashok Kar, Teacher

The committee has also decided to:

☑ Approve the study protocol in the present from.

☐ Conditionally approve the study protocol subject to .....

☐ Reject the proposal for the following reasons .....

You are required to:

i) Inform the committee about the progress of the study and compliance of ethical guidelines.
ii) Notify the committee regarding any serious adverse events occurring in the course of the study.
iii) Inform and seek approval of the committee about any changes in the protocol prior to their implementation.
iv) Submit the final report to the committee in every case.
v) None of the Study team members including PI were not participated in the voting process.

This Ethics committee is working in accordance with the ICH-GCP, ICMR and New Clinical Trail Rules 2019 guidelines and other applicable regulations as laid down by the DCGI from time to time.

Yours truly,

sd/- 10/12/2021

Chairperson/Member Secretary IEC
Medical College, Kolkata

MEMBER SECRETARY
IEC, MEDICAL COLLEGE
KOLKATA

Ref No. MC/KOL/IEC/NON-SPON/1675/11/2022

THE WEST BENGAL UNIVERSITY OF HEALTH SCIENCES

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Form for submitting 'RESEARCH PROPOSAL' (SYNOPSIS) on the thesis for MD / MS / MDS / M. Sc (Nursing) / MPT / MD (Hom.) / MD (Ayur.) / MASLP etc. *(tick)*

in the subject MS OBSTETRICS AND GYNAECOLOGY **for the session of 2021 to 2024**

1. Name of the Student (Block Letters) :: SWADHA PANDEY
2. WBUHS Reg. No. & Year (Mandatory) :: A/F
3. Name of the Institution :: MEDICAL COLLEGE AND HOSPITAL
4. Cell Phone / E-mail / Land line No. :: 7908851587, drswadha@gmail.com
5. Name of the Guide with Proper designation :: Dr. PALASH MAZUMDER ASSOCIATE PROFESSOR
6. Name of the Co-Guides (if any) with proper designation ::
7. Proposed 'TITLE' of the thesis *(in Block Letters) Leave one space between words*

LETROLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS

8. Proposed place of work *(in Block letters) Leave one space between words*

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

9. Bank Draft Particulars	Name of the Bank	Branch	Amount (Rs.)	Draft No.	Date
			Rs. 400/-		

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Swadha Pandey
Signature of the candidate
Forwarded

Forwarded
Palash Mazumder
Signature of Guide with Official Seal & date

Associate Professor
Dept. of Obst. & Gynae
Medical College Hospital
Kolkata
Signature of other Guide with Official Seal & date

Countersigned
Subir Kumar Bandyopadhyay
Signature of the HOD 09/12/2022
with official seal & date

Prof. & Head
Eden Hospital
Medical College, Bengal

Countersigned
16/12/2022
Signature of the Head of the Institute
with official seal & date
Principal
Medical College & Hospital
88, College Street, Kol-73

Office of the Principal
Medical College, Kol-73

To

The Chairman, Institutional Ethics Committee,

Medical College and Hospital, Kolkata.

(Through proper channel)

Subject: Application for Ethics committee clearance of the research proposal for the in M.S Obstetrics and Gynaecology, session 2021-2022.

Respected Sir/Madam,

I, Dr Swadha Pandey, a first year post graduate trainee (Junior Resident) of The Department of Obstetrics and Gynaecology, Medical College and Hospital, Kolkata would like to propose to conduct a study entitled "LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS" for M.S in Obstetric and Gynaecology, Session 2021-2022.
As per the norms of the West Bengal University of Health Sciences, I am here by submitting the followings for clearance from Institutional Ethics Committee, Medical College and Hospital, Kolkata. 1. Study Protocol. 2. Study Proforma. 3. Patient Consent form. Kindly consider and do the needful.

Yours' Sincerely

Dr. Swadha Pandey

1st Year PGT

Dept. of Obstectrics and Gynaecology

Cont : 7908851587

Palash Mazumder
Signature of the Guide

Associate Professor
Dept. of Obst. & Gynae
Medical College Hospital
Kolkata

Subir Kumar Bhattacharyya 9/12/22
Signature of the Head of Deptt, Obstetrics and Gynaecology

Prof. & Head
Eden Hospital
Medical College, Bengal

To

The Chairman, Scientific Advisory Committee,

Medical College and Hospital, Kolkata.

Through proper channel

Subject: Application for Scientific Advisory committee clearance of the research proposal for THESIS in M.S Obstetrics and Gynaecology, session 2021-2022

Respected Sir/Madam,

I, Dr Swadha Pandey, a first year post graduate trainee (Junior Resident) of The Department of Obstetrics and Gynaecology, Medical College, Kolkata would like to propose to conduct a study entitled "LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS" for M.S in Obstetrics and Gynaecology, Session 2021-2022.
In accordance with the norms of the West Bengal University of Health Sciences, I am here by submitting the followings for clearance from Institutional Ethics Committee, Medical College, Kolkata. 1. Study Protocol. 2. Study Proforma. 3. Patient Consent form.
Kindly consider and do the needful.

Yours' Sincerely
Dr. Swadha Pandey
1st Year PGT
Dept. of Obstectrics and Gynaecology
Cont : 7908851587

Signature of the Guide

Associate Professor
Dept. of Obst. & Gynae
Medical College Hospital
Kolkata

01.12.22

Signature of the Head of Deptt, Obstectrics and Gynaecology

Prof. & Head
Eden Hospital
Medical College, Bengal

INSTITUTIONAL ETHICS COMMITTEE FOR HUMAN RESEARCH
(Registration No. ECR/287/Inst/WB/2013)
MEDICAL COLLEGE AND HOSPITAL, KOLKATA 88, COLLEGE STREET, KOLKATA-700073
033-2212-3853
Email: ecmckol@yahoo.co.in

To

The Principal

Medical College,

Kolkata 88, College Street, Kolkata -73

(Through proper channel)

Subject : Authorization regarding the submission of research proposal for the THESIS for M.S in

OBSTETRICS AND GYNAECOLOGY, Session 2021-2022

Respected Sir/Madam,

With respect to the subject cited above,I would like to kindly inform you that I am submitting the research proposal for my thesis entitled "AN OBSERVATIONAL,COMPARITIVE STUDY BETWEEN LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

The detailed protocol along with the informed consent documents, case report forms and other relevant documents are attached. Should any further information be needed, I will be obliged to provide the same.

Kindly consider the same and give the needful permission.

Thanking you.

Yours' Sincerely

Dr. Swadha Pandey Swadha Pandey

1st Year PGT

Dept. of Obstectrics and Gynaecology (Cont : 7908851587)

Parash Mazumder
Associate Professor
Dept. of Obst. & Gynae
Medical College Hospital
Kolkata

01.12.22
Prof. & Head
Eden Hospital
Medical College, Bengal

SYNOPSIS FOR THESIS ON

" LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

GUIDE

Dr. Sukumar Mitra

Associate Professor

Department of Obstetrics and Gynaecology

Medical College and Hospital, Kolkata

NAME OF THE STUDENT

Dr. Swadha Pandey

Post Graduate student (1st Year)

Department of Obstetrics and Gynecology

Medical College and Hospital, Kolkata

A) SUMMARY:

1. a) NAME OF CANDIDATE: SWADHA PANDEY

DESIGNATION Post graduate student (1st year)

Department of Obstetrics and Gynaecology

Medical College, Kolkata.

b) PLACE OF PROPOSED RESEARCH WORK AND NAME OF INSTITUTE: Institution based study conducted at OPD of Department of Obstetrics and Gynaecology, Medical College Kolkata.

c) BROAD AREA AND SPECIFIC AREA: Clinical; Department of Obstetrics and Gynaecology .

2. NAME OF PROPOSED SUPERVISORS:

GUIDE : Dr. Sukumar Mitra

Associate Professor

Department of Obstetrics and Gynaecology,

Medical College and Hospital, Kolkata.

3. PROPOSED TOPIC OF RESEARCH:" LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

4. OBJECTIVE OF PROPOSED RESEARCH:

- Primary Objectives:
  1. Effect of Letrozole and Dienogest in relieving of Chronic pelvic pain in patients.
  2. Reduction of Dysmenorrhea in patients treated with Letrozole and Dienogest.
- Secondary Objectives:
  1.Reduction in the size of Endometrioma
  2.To compare the side effects of the drugs
  3. Patient satisfaction with relation to symptoms of pelvic endometriosis in the two study groups.

5. BACKGROUND OF THE PROPOSED STUDY:

Endometriosis is a disease with a high prevalence that primarily affects women of childbearing age. This condition brings an important physical and emotional burden on sufferers and this is why it requires proper and timely medical management. At present there are several first-line drugs available for the management of symptoms and disease control. In the world literature, several studies have reported that demonstrate the effectiveness of different groups of drugs such as oral contraceptives, progestins, aromatase inhibitors, GnRH analogues and danazol.[1]

Letrozole is a third-generation aromatase inhibitor. As there is aberrant aromatase production by endometriotic stromal cells and the growth and regression of endometriosis is estrogen-dependent, the use of letrozole to alleviate symptoms of endometriosis especially in recurrent cases is a promising medical intervention.

Dienogest is a fourth-generation progestin which is being used for the treatment of endometriosis due to its antiproliferative and antiangiogenic properties on endometrial tissue. The present study was conducted to compare the effects of letrozole and dienogest on endometrioma recurrent after surgery.Dienogest, demonstrating a favorable safety profile and efficacy along with a significant reduction of the symptoms of the disease by its anti-inflammatory, and anti-proliferative anti angiogénic action in the endometrial tissue. Dienogest However, although the therapeutic properties of this drug are known, studies are needed to compare its effectiveness with the effectiveness of other therapeutic agents as Aromatase inhibitors.

That is why the primary objective of this study is to compare the alleviation of chronic pelvic pain and dysmenorrhea by use of Letrozole (2.5mg daily) and Dienogest (2 mg once daily) in the management of endometriosis. The results will be analyzed and the findings in the study will hopefully serve as a tool to define new therapeutic conduct in the management of endometriosis.

6. METHODOLOGY: This will be a prospective observational study and will be done in Indian population visiting Medical College and Hospital, Kolkata consisting diagnosed case of endometrioses.

7. EXPECTED OUTCOME: Both Dienogest and Letrozole are effective in control of chronic pelvic pain and dysmenorrhea in endometriosis and their efficacy in pain reduction is comparable.

Regarding the parameters of reduction in size of endometrioma and pain both drugs are comparable with acceptable side effects and optimum satisfaction.

B) OUTLINE OF PROPOSED RESEARCH TOPIC:

1.PROPOSED TOPIC OF RESEARCH:"LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

2. OBJECTIVE OF RESEARCH:

a. Primary Objectives:
   1. Effect of Letrozole and Dienogest in relieving of Chronic pelvic pain in patients.
   2. Reduction of Dysmenorrhea in patients treated with Letrozole and Dienogest.

b. Secondary Objectives:
   1.Reduction in the size of Endometrioma
   2.To compare the side effects of the drugs
   3. Patient satisfaction with relation to symptoms of pelvic endometriosis in the two study groups.

3. RESEARCH HYPOTHESIS:

Endometriosis is the presence of functioning endometrial glands and stroma outside of the endometrial cavity. It represents one of the most challenging gynecologic conditions to manage given its insidious onset, surgical diagnosis, association with pelvic pain and infertility, and often progressive nature. Endometriosis is a chronic disease affecting at least 10% of reproductive-aged women, but is found in approximately 40% of infertile women and up to 90% of women with pelvic pain.

The classic triad of endometriosis symptoms, dysmenorrhea, dyspareunia, and dyschesia, raises clinical suspicion for this disorder.

Endometriosis is an estrogen-dependent chronic inflammatory disease affecting the health and well-being of 5%–10% of women of reproductive age, with a prevalence of 5%–50% in infertile women and >33% of women with chronic pelvic pain. Endometriosis is characterized by the presence of ectopic endometrial implants typically occurring in the pelvis, most commonly in the ovaries, pelvic peritoneum, uterosacral ligaments, pouch of Douglas, and rectovaginal septum. Patients can present with a wide range of symptoms; however, the cardinal clinical features are infertility and chronic pelvic pain.

The definitive pathogenesis of endometriosis is still unknown, but retrograde menstruation, proposed by Sampson in the 1920s, is still considered the most widely accepted theory, although many points remain poorly understood concerning this theory.[5] Of note, the incidence of retrograde menstruation is similar in women with and without endometriosis, so the pathogenesis seems to be a multifactorial mechanism comprising functionally different endometrial tissue in addition to altered immunity and other molecular abnormalities allowing the survival of the regurgitated endometrial debris. Subsequently, these endometrial implants go through various sequential events for the disease to develop.

Endometriosis is an estrogen-dependent chronic inflammatory disease affecting 5%–10% of reproductive-age women, with a prevalence of 5%–50% in infertile women and >33% of women with chronic pelvic pain. Third-generation aromatase inhibitors (AIs) are approved adjuvants for the treatment of estrogen receptor-positive breast cancer. Molecular studies have revealed the presence of aromatase P450, the key enzyme in the biosynthesis of ovarian estradiol, inside the endometriotic tissue, indicating local synthesis of estradiol. Thereby, AIs represent an appealing medical option for the management of different aspects of this enigmatic disease, especially pelvic pain and infertility. Accordingly, this review aims to evaluate the potential role of AIs in the treatment of endometriosis-associated symptoms, mainly pain and infertility[4,5]. Notably, several studies have demonstrated that the combination of AIs with conventional therapy as oral contraceptive pills, progestins, or gonadotropin-releasing hormone analogs can be used to control endometriosis-associated pain and pain recurrence in premenopausal women, particularly those with pain due to rectovaginal endometriosis refractory to other medical or surgical treatment. Some case reports have shown promising results in the treatment of postmenopausal endometriosis as first-line treatment, when surgery is contraindicated, or as second-line treatment in the case of postoperative recurrence. Third-generation AIs, especially letrozole, have challenged clomiphene citrate as an ovulation-induction agent in patients with polycystic ovary syndrome and in cases of unexplained infertility. However, few studies are available regarding the use of AIs to treat endometriosis-associated infertility. Therefore, larger multicenter randomized trials using AIs for the treatment of endometriosis-associated infertility are needed to clarify its effect. The safety of AIs for ovulation induction or superovulation has generated a lively discussion. Data from recent retrospective and prospective studies have supported its safety[8,9,10].

As endometriosis is an estrogen-dependent disease, conventional treatments utilized for many years aimed to act indirectly to create an estrogen-deficient state, eg, gonadotropin-releasing hormone agonists (GnRHas) and combined oral contraceptive pills or counteracting estrogen action, eg, progestins, eventually resulting in inhibition of the endometrial implant growth and alleviation of symptoms.

Aromatase P450 is the key enzyme for ovarian estrogen biosynthesis. It catalyzes the conversion of androstenedione and testosterone produced in the ovarian theca cells to estrone and estradiol (E_2) in the ovarian granulose cells. Recently, there has accumulated a body of evidence demonstrating that endometriotic lesions express aromatase and are able to synthesize their own E_2. In view of this observation, the use of aromatase inhibitors (AIs) for the management of endometriosis is an appealing concept. Accordingly, this review aims to evaluate the potential role of AIs in the treatment of endometriosis-associated symptoms, particularly pain and infertility[8].

Dienogest, an oral progestin has potent progestogenic efficacy combined with moderate estrogen suppressive effects, together with anti-inflammatory, antiproliferative, and antiangiogenic effects that effectively reduce the growth of endometrial-like tissue. It is associated with minimal spotting and breakthrough bleeding. Long term use of Dienogest alone produces amenorrhea often unacceptable amongst women.

4. BACKGROUND OF RESEARCH:

a) RATIONALE OF STUDY (JUSTIFICATION OF PRESENT STUDY) : Endometriosis is a disease with a high prevalence that primarily affects women of childbearing age. This condition brings an important physical and emotional burden on sufferers and this is why it requires proper and timely medical management. The symptoms of pain and dysmenorrhea hamper daily activities, life style, sexual life etc. which affects the mental health of the affected individuals. Both the drugs are used in the management of pain and control the progression of the disease, but no one drug is considered to be the first line or choice in treatment of endometriosis. This study may help in establishing better pharmacological management in Endometriosis.

b) INTRODUCTION :

Endometriosis, the presence of endometrial glands and stroma outside of the endometrial cavity, represents one of the most challenging gynecologic conditions to manage given its insidious onset, surgical diagnosis, association with pelvic pain and infertility, and often progressive nature. Endometriosis is a chronic disease affecting at least 10% of reproductive-aged women, but is found in approximately 40% of infertile women and up to 90% of women with pelvic pain. The classic triad of endometriosis symptoms, dysmenorrhea, dyspareunia, and dyschesia, is clinical suspicion for this disorder.[1,2]

Endometriosis is a benign inflammatory disease affecting women of reproductive age, defined as the presence of endometrial glands and stroma outside the uterus. Endometriotic lesions may have various locations; they are found more frequently on the pelvic peritoneum, on the ovaries, in the rectovaginal septum, on the uterosacral ligaments, in the vesico-uterine fold, and more rarely in the bowel, diaphragm, umbilicus, pericardium and pleura . The exact pathogenesis is incompletely understood.

Three theories have been proposed to explain the histogenesis of endometriosis:

1. Ectopic transplantation of endometrial tissue (Sampson's Theory): The transplantation theory, originally proposed by Sampsonin the mid-1920s, is based on the assumption that endometriosis is caused by the seeding or implantation of endometrial cells by transtubal regurgitation during menstruation

2. Coelomic metaplasia: The transformation (metaplasia) of coelomic epithelium into endometrial tissue has been proposed as a mechanism for the origin of endometriosis

3. The induction theory: The induction theory is, in principle, an extension of the coelomicmetaplasia theory. It proposes that an endogenous (undefined) biochemical factor can induce undifferentiated peritoneal cells to develop into endometrial tissue.

No single theory can account for the location of endometriosis in all cases.[2,3,4]

Infertility: Many arguments support the hypothesis that there is causal relationship between the presence of endometriosis and infertility. Some of them include; Increased prevalence of endometriosis in infertile women (33%) when compared to women of proven fertility;trend toward a reduced MFR in infertile women with minimal to mild endometriosis when compared to women with explained fertility.Endometriotic ovarian cysts that negatively affect the rate of spontaneous ovulation.Increased MFR and cumulative pregnancy rate after surgical removal of minimal to mild endometriosis.When endometriosis is moderate or severe, involving the ovaries and causing adhesions that block tubo-ovarian motility and ovum pickup, it is associated with infertility.[3,4]

Endocrinologic Abnormalities : Endometriosis has been associated with anovulation, abnormal follicular development with impaired follicle growth, reduced circulating E2 levels during the pre ovulatory phase, disturbed luteinizing hormone (LH) surge patterns, premenstrual spotting, the luteinized unruptured follicle syndrome, and galactorrhea and hyperprolactinemia.

In many women with endometriosis, no abnormality is detected during the clinical examination. However, the vulva, vagina, and cervix should be inspected for any signs of endometriosis, although the occurrence of endometriosis in these areas is rare (e.g., episiotomy scar). Other signs of possible endometriosis include uterosacral or cul-de-sac nodularity, lateral or cervical displacement caused by uterosacral scarring, painful swelling of the rectovaginal septum, and unilateral ovarian (cystic) enlargement. In more advanced disease, the uterus is often in fixed retroversion, and the mobility of the ovaries and fallopian tubes is reduced. Evidence of deeply infiltrative endometriosis (deeper than 5 mm under the peritoneum) in the rectovaginal septum with cul-de-sac obliteration or cystic ovarian endometriosis should be suspected by clinical documentation of uterosacral nodularities during menses. In these cases, black blue coloured lesions can sometimes be observed in the vagina during speculum examination.

Imaging:As endometriosis symptoms are non specific and the clinical examination may have false negative results, the modality of diagnosis is medical imaging. The gold standard for diagnosis of endometriosis remains laparoscopic visualization of lesions with histologic confirmation.

Ultrasound : The guidelines from European Society of Reproduction and Embryology and American College of Obstetricians and Gynecology (ACOG) recommend transvaginal ultrasound as the first imaging step in the diagnostic work up of women with suspected endometriosis. However the sensitivity and specificity of TVUS are strongly dependent on the interest and experience of the sonographer and the quality of the sonography equipment.

TVUS is reliable in detecting or excluding the presence of an endometrioma (sensitivity=79%, specificity=94%)

TVUS can detect deep endometriotic lesions with moderate reliability (sensitivity=79%< specificity=94%)

The absence of endometriosis on TVUS does not rule out the presence of peritoneal or deep endometriosis. Based on the patients' symptoms and clinical examination, a diagnostic laparoscopy should be considered.[18]

Other Imaging Techniques: Computes Tomography(CT) and MRI can be used to provide additional and confirmatory information, but they are not considered first line imaging modalities due to high costs and their added value is unclear.MRI has a good sensitivity and specificity for diagnosis of deep endometriosis and endometriomas but the value in addition to TVUS is limited. A negative MRI does not rule out peritoneal endometriosis because lesions are identified only if they are haemorrhagic, greater than 5 mm or when associated with extensive adhesions distorting the normal anatomy.

Blood And Other Tests: There is no blood test available for the diagnosis of endometriosis

CA125 Levels of CA125, glycoprotein from the coelomic epithelium and common to most nonmucinous

epithelial ovarian carcinomas, have been found to be significantly higher in women with moderate or severe endometriosis and normal in women with minimal or mild disease . Compared with laparoscopy, measurement of serum CA125 levels has no value as a diagnostic tool.

Laparoscopy: Unless disease is visible in the vagina or elsewhere, laparoscopy can be used. During diagnostic laparoscopy, the pelvic and abdominal cavity should be systematically investigated for the presence of endometriosis. Endometriosis can be treated during laparoscopy, thus combining diagnosis and therapy.The laparoscopic findings include peritoneal lesions, ovarian endometriotic cysts and deep endometriosis invading the peritoneal surface with a depth of atleast 5 mm.

Peritoneal Endometriosis: Characteristic findings include typical ("powder-burn" or "gunshot") lesions on the serosal surfaces of the peritoneum. These lesions are black, dark brown, or bluish nodules or small cysts containing old hemorrhage surrounded by a variable degree of fibrosis. Endometriosis can appear as subtle lesions, including red implants (petechial, vesicular, polypoid, hemorrhagic, red flame like), serous or clear vesicles, white plaques or scarring, yellow-brown discoloration of the peritoneum, and sub ovarian adhesions. Histologic confirmation of the laparoscopic impression is essential for the diagnosis of endometriosis, not only for subtle lesions but also for typical lesions reported to be histologically negative in 24% of cases.

Histologic Confirmation Positive histology confirms the diagnosis of endometriosis; negative histology does not exclude it. In case of ovarian endometrioma (>4 cm in diameter) and in deep endometriosis, histology is recommended to exclude rare instances of malignancy.Microscopically, endometriotic implants consist of endometrial glands and stroma, with or without hemosiderin-laden macrophages. Different types of lesions may have different degrees of proliferative or secretory glandular activity. Vascularization, mitotic activity, and the three-dimensional structure of endometriosis lesions are key factors. Although it may be asymptomatic, endometriosis often causes pain symptoms and infertility. Pain negatively influences quality of life (QoL), working efficiency, personal relations, and sexual life of patients. Transvaginal ultrasonography (TVS) is the gold standard technique for the diagnosis of deep endometriosis and ovarian endometrioma; magnetic resonance imaging (MRI) may be used when the gynecologists have no experience in the ultrasonographic diagnosis of endometriosis or when the findings of ultrasonography are unclear. In

any case, the certain diagnosis of endometriosis is only obtained with the histological confirmation of endometrial stroma and glands.[5]

Endometriosis is a chronic disease . Medical therapy is often the first line of management for women with endometriosis in order to ameliorate symptoms or to prevent post-surgical disease recurrence. Currently, there are several medical options for the management of patients with endometriosis.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of chronic inflammatory conditions, being efficacious in relieving primary dysmenorrhea. The rationale for use of NSAIDs in endometriosis is based on their analgesic and anti-inflammatory effect.

Combined oral contraceptives (COCs) and progestins (oral, vaginal ring or transdermal patch), either sequential or continuous, are effective first-line hormonal options. They are commonly used to manage endometriosis-related dysmenorrhea and pain symptoms, even for some practical advantages, including contraception, long-term safety and control of menstrual cycle. In fact, several randomized controlled trials (RCTs) demonstrated that they succeed in improving pain symptoms in the majority of patients, are well tolerated and not expensive. Second-line therapy is represented by gonadotropin-releasing hormone (GnRH) agonists.

Progestins, which are synthetic progestogens, are available in various formulations (oral tablets, depot injections, implants, or releasing intrauterine systems), and are increasingly used as monotherapy for the treatment of women affected by endometriosis. These compounds reduce the frequency and increase the amplitude of pulsatile gonadotropin-releasing hormone (GnRH) release, causing a decrease of follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion. Suppressing the ovarian steroidogenesis, causing subsequent anovulation and reducing serum levels of ovarian steroids, they cause decidualization and acyclicity of both normal and ectopic endometrium.

Medroxyprogesterone Acetate is the most studied agent. It is effective in relieving pain starting at the dose of 30mg oer day, increasing the dose based on the clinical response and clinical response according to data from non randomized trials. Although it is effective, it is not indicated in infertile women because it produces profound amenorrhea and anovulation, and a varying length of time is required to resume after discontinuation of therapy.

Aromatase inhibitors cause a decrease in estrogen concentration, making them useful for treating estrogen-dependent conditions, including endometriosis. The aromatase enzyme complex itself is composed of two polypeptides. The first is aromatase cytochrome P450 (CYP450arom), which is the product of a single gene, CYP19. The second is a flavoprotein, NADPH–cytochrome P450 reductase, and is ubiquitously distributed in most cells.[7,8]

There have been three generations of AIs. The first-generation inhibitor, glutethimide, induces a medical adrenalectomy, which, in addition to this desired effect, causes many side effects, including lethargy, skin rashes, and nausea. The second-generation inhibitors include fadrozole and formestancel, which are more selective and have fewer side effects. The route of administration for these medications is intramuscular. The third-generation AIs, including letrozole, anastrazole, and examestande, are triazole derivatives, which are selective, reversible, and potent, making them ideal for use in clinical practice.

Dienogest is a steroidal fourth-generation selective progestin that combines the pharmacologic properties of 19- nortestosterone and derivatives of progesterone. A nonethinylated progestin that is structurally related to testosterone , DNG has antiandrogenic activity and thus can improve androgenic skin-related side effects. At the pharmacokinetic level, DNG is absorbed rapidly after oral intake with approximately 90%

bioavailability [6], and it is exclusively bound to albumin (90%) and not to sex hormone-binding globulin or corticoid binding globulin . It is metabolized in the liver mainly by cytochrome P450 isoform 3A4 (CYP3A4) followed by rapid excretion of its inactive metabolites, and does not accumulate in the body .

Dienogest has a profound local effect on endometriotic lesions, with little androgenic, estrogenic, glucocorticoid, or mineralocorticoid activity and minimal impact on metabolic parameters [7]. Studies have shown that DNG has both ananovulatory and an anti proliferative effect, while inhibiting the secretion of cytokines in the stroma of endometrial cells . Dienogest modulated prostaglandin (PG) production and metabolism (PGE2, PGE2 synthase, cyclooxygenase-2, and microsomal PGE synthase-1) in a way that is anti-inflammatory.[11]

Hormonal contraceptives containing both Ethinyl Estradiol (EE) and progestin can be used in a cyclic or continuous fashion for the treatment of endometriosis. Continuous use appears to result in better pain control . The most widely accepted pharmacologic theory is that OCs prevent ovulation and suppress the progesterone-driven proliferation of the secretory endometrium during the luteal phase, thereby resulting in a decrease in the volume of menstrual fluid and prostaglandin synthesis and decrease endometriosis associated pain.

The combination of Dienogest/ Ethinyl estradiol acts by primary mechanism of inhibition of ovulation (by suppression of gonadotrophins) and changes in the cervical secretion (blocking the entry of sperm into uterus). Also because of the presence of cyclical bleeding in constrast to amenorrhea with the use of dienogest alone , this combination may be more acceptable among Indian women. For the majority of users the cycle becomes more regular, menstruation less painful and bleeding is lighter.The latter also might have a beneficial effect in decreasing occurrence of iron deficiency. Dienogest has other beneficial effects as it exerts an anti androgenic activity leading to positive effect on the skin and to reduction of acne and sebum production.

Progesteone antagonists(PRAs) and Selective Progesterone Receptor Modulators(SPRMs) may suppress endometriosis based o their antiproliferative effect on the endometrium without the risk for hypooetrogenism or bone loss that occurs with GnRH treatment.Four PRAs/SPRMs have been approved by the FDA : Mifepristone, Ulipristal Acetate, Gestrinone and Asoprisnil.

Danazol, a GnRH analogue cause suppression of GnRH or gonadotropin secretion, direct inhibition of steroidogenesis, increased metabolic clearance of estradiol and progesterone, direct antagonistic and agonistic interaction with endometrial androgen and progesterone receptors. The multiple effects of danazol produce a high androgen, low estrogen environment that does not support the growth of endometriosis , and the amenorrhea that is produced prevents new seeding of implants from the uterus into the peritoneal cavity. The most common side effects include weight gain, fluid retention, acne, oily skin, atrophic vaginitis, hirsutism, hot flushes, reduced libido, fatigue and emotional instability.[11]

Gonadotropin Releasing Hormonr Agonists bind to pituitary GnRH receptors and stimulate LH anf FSH synthesis and release. The agonists have a much longer biological half-life (3–8 hours) than endogenous GnRH (3.5 minutes), resulting in the continuous exposure of GnRH receptors to GnRH agonist activity. This exposure causes a loss of pituitary receptors and downregulation of GnRH activity, resulting in low FSH and LH levels.Consequently, ovarian steroid production is suppressed, providing a medically induced and reversible state of pseudomenopause. Various GnRH agonists have been developed and used in treating endometriosis. These agents include *leuprolide*, *buserelin*, *nafarelin*, *histrelin*, *goserelin*, *deslorelin*, and *triptorelin*.These drugs are inactive orally and must be administered intramuscularly, subcutaneously, or by intranasal absorption. GnRH agonists should not be prescribed to girls who have not yet attained their maximal bone density, as some concern remains about the long term effect of GnRH on bone loss.[11]

Aromatase Inhibitors **e.g** Anastrozole, Letrozole. There is concern with the use of aromatase inhibitors in the treatment of premenopausal women because these drugs are known to stimulate ovulation and continuous administration can result in the development of functional cysts. This side effect can be prevented by combining them with ovarian suppressing drugs such as OCs or progestins.[13]

Gonadotropin releasing Hormone Antagonist inhibit the action of endogenous GnRH through competitively and irreversibly binding to GnRH receptors in the pituitary gland. They are available as injectables (ganirelix, cetrorelix) and increasingly as oral non peptide forms (elagolix, abarelix, ozarelix).[11]

Surgical Treatment : The goal of surgery is to excise all visible endometriotic lesions and associated adhesions—peritoneal lesions, ovarian cysts, deep rectovaginal endometriosis—and to restore normal anatomy. Laparoscopy is preferred over laparotomy because the two techniques are equally effective and laparoscopy is associated with quicker recovery, better cosmesis, less postoperative pain, decreased costs, lower morbidity, and fewer postoperative adhesions.

GAP IN EXISTING STUDY:

Though Dienogest is first line drug for treatment of endometriosis, no one drug is considered to be best for management of chronic pelvic pain in endometriosis and studies are ongoing in search for more effective drug with better safety profile and least possible side effects with preservation of normal reproductive physiology.

REVIEW OF LITERATURE:

1.This randomized controlled study was conducted on 38 women having recurrence of endometrioma after surgery. They were randomly assigned to receive either letrozole (2.5 mg daily) or dienogest (2 mg once daily) for 6 months. Size of the endometrioma was measured by transvaginal ultrasound and the pain (dysmenorrhoea) was measured on a visual analog scale (VAS) of 0-10, prior to treatment and after 3 and 6 months of treatment. Results: The mean size of endometrioma was reduced from a baseline of 6.06±2.40 cm to 5.23±1.37 cm and to 4.59±1.25 cm after 3 and 6 months of treatment with letrozole. While with dienogest the reduction was from a baseline of 6.67±1.31 cm to 4.83±1.50 cm and to 3.80±1.34 cm after 3 and 6 months of treatment. The difference between the two groups was not statistically significant but dienogest yielded better result in terms of effect size. Decrease in pain dysmenorrhoea) was highly significant with both the drugs.[6]

2. A prospective non comparative observational study was conducted in the Department of Reproductive Endocrinology and Infertility of BSMMU on 30 women with ovarian endometrioma during the period of April 2019 to March 2020. Women were treated with aromatase inhibitor (letrozole) 2.5 mg, norethisterone 5 mg, calcium 1200 mg, and vitamin D 800 IU daily for 6 months. Transvaginal ultrasound was performed at baseline, 3 months and 6 months after treatment to assess the mean diameter and volume of endometriomas. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0. Results: More than 50% reduction in volume occurred in 90% of endometrioma. In one (3.3%) case endometrioma disappeared

completely after 6 months. There was statistically significant reduction of size of endometrioma (estimated by mean diameter and volume) and pain. Volume decrease was linearly related to baseline endometrioma volume and inversely related to baseline body mass index (BMI). The side effects were mild and well tolerated by the patients. [15]

3. This randomized prospective open-label study compared the efficacy in treating pain symptoms and the tolerability of letrozole combined with either norethisterone acetate or triptorelin. Methods: Women with pain symptoms caused by rectovaginal endometriosis were treated with letrozole(2.5 mg/day) and were randomized to also receive either oral norethisterone acetate (2.5 mg/day; group N) or intramuscular injection of triptorelin (11.25 mg every 3 months; group T). The scheduled length of treatment was 6months. A visual analogue scale and a multidimensional categorical rating scale were used to assess the severity of pain symptoms. The volume of the endometriotic nodules was estimated by ultrasonography using virtual organ computer-aided analysis. Adverse effects of treatment were recorded .Results: A total of 35 women were randomized between the two treatment protocols. Significantly more patients in group N rated their treatment as satisfactory or very satisfactory (64.7%) as compared to group T (22.2%; p = 0.028). The intensity of both non-menstrual pelvic pain and deep dyspareunia significantly decreased during treatment in both study groups, though no statistically meaningful difference between the two groups was apparent. Reduction in the volume of endometriotic nodules was significantly greater in group T than in group N. Interruption of treatment due to adverse effects significantly differed between the groups, with 8 women in group T (44.4%) and 1 woman in group N (5.9%) interrupting treatment (p = 0.018).Similarly, 14 women included in group T (77.8%) and 6 women included in group N (35.3%) experienced adverse effects of treatment (p = 0.018). During treatment, mineral bone density significantly decreased in group T but not in group N.[14]

METHODOLOGY:

MATERIALS AND METHODS :

a) STUDY DESIGN : The study will be a prospective observational study. The patients will be distributed in two groups in this study that will be randomized by computerized randomization chart.

b) STUDY SETTING AND TIMELINE : The study will be conducted from Jan 2023 to February for a period of 14 months.

- Preparatory phase: 1 month
- Data collection phase: 6 months
- Follow up phase: 6 months

- Data analysis phase: 1 months

c) PLACE OF STUDY : The study will be conducted in gynaecology OPD in Department of Obstetrics and Gynaecology, Medical College and Hospital, Kolkata

d) PERIOD OF STUDY : 14 months (Jan 2022 Feb 2023).

e) STUDY POPULATION : Patients out-patient departments during the study period who are clinically or sonologically diagnosed cases of endometriosis.

f) SAMPLE SIZE : Assuming p value <0.05 to be significant and considering effect to be two sided, we get Z_{α} =1.96; assuming power of study to be 90% we get $Z_{1-\beta}$ = 1.28; considering an effect size (Difference in Mean reduction in Size (mean of max diameter) of endometrioma (cm) after 3 months) of 0.48 to be statistically significant we get $n > 2(Z_{\alpha} + Z_{1-\beta})2 \times SD2/d2$ we get n = 23. Hence minimum 23 patients will be taken in each group. We have considered 20% drop out rate and will take 28 samples per group. Hence Total Sample Size is coming 56 but we will round it off and take Total Sample Size to be 60, taking 30 in each group.

z_{α} (the Value of the standard normal variate at 5% error) =1.96

$z_{1-\beta}$ (the Value of the standard normal variate at 90% power) =1.28

Mean reduction in Size (mean of max diameter) of endometrioma (cm) after 3 months Group 1 = 1.49

Mean reduction in Size (mean of max diameter) of endometrioma (cm) after 3 months minute Group 2 = 1.01

d=Effect Size = (1.49-1.01) = 0.48

SD = Pooled Standard Deviation Assumed to be 0.5

$n > 2(Z_{\alpha} + Z_{1-\beta})2 \times SD2/d2$

$= 2(1.96 + 1.28)2 \text{ X } 0.52/(0.48)2 = 22.80 \sim= 23.$

Required samples = 1.20 x 23 = 27.6 ~= 28.

g) CASE CONTROL REQUIRED OR NOT : No separate control group will be required.

h) INCLUSION CRITERIA :

1.Patients from out-patient department during the study period who are clinically, sonologically or surgically diagnosed cases of endometriosis.

2. Women in the age group 20-40 years.

3. Patients who are willing to participate in the study.

EXCLUSION CRITERIA :

1. Patients with desire for pregnancy

2. Patients with associated pelvic diseases like fibroid uterus, PIDs, suspected malignancies.

3.Teenage patients

4.Patients with liver disorders, circulatory diseases (past and present) namely arterial and venous thrombosis, severe hypertension, h/o stroke, heart disease: valvular, ischaemic, diabetes with vascular complications, migraine with focal neurologic symptoms.

5. Patients not willing to participate in the study.

i) STUDY VARIABLES : Chronic pelvic pain, Dysmenorrhea, Dyspareunia, Size of the endometrioma, Side effects and Acceptability .

j) LABORATORY INVESTIGATIONS AND PROCEDURES :

Complete blood count, Urine RE/ME and culture and sensitivity, Liver function profile(LFT), Sugar(FBS/PPBS), S. Urea/ Creatinine, Lipid Profile

USG- Transvaginal sonography

k) OUTCOME DEFINITION AND PARAMETERS :

- Reduction and control of dysmenorrhea by using VAS scoring system
- Reduction in endometriosis associated pelvic pain using VAS scoring system
- Reduction in the size of endometrioma on transvaginal USG.
- Safety and long term use
- Tolerability and patient satisfaction in terms of compliance, withdrawal rates, quality of life.

l) STATISTICAL ANALYSIS : Categorical variables will be expressed as Number of patients and percentage of patients and compared, if required, using Pearson’s Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate.

Continuous variables will be expressed as Mean ± Standard Deviation and compared using unpaired t test if the data follows normal distribution or Median and Inter-quartile Range and compared using Mann-Whitney U test if the data does not follow normal distribution. The statistical software SPSS version 28 will be used for the analysis.An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it will be considered as significant.

n) ETHICAL CLEARANCE : The study protocol, patient information sheet and the informed consent form will be submitted to the Institutional Ethical Committee (IEC) of Medical College Kolkata. Study will be started after approval from IEC.

m) WORK PLAN : Jan 2023– Feb 2024

1.Data collection period 6 months.

Patients will be divided equally into two study groups, first group in treatment with dienogest and the second group being treated on dienogest/ethinyl estradiol combination..

2. Follow up of patients- at 1 month, 3 month and 6 months.All patients will participate only after giving written informed consent.Comparison of end result in both study group, Preparation of thesis sample, Final proof reading and printing in last 1 month.

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CASE RECORD FORM

DEPARTMENT OF OBSTETRIC & GYNAECOLOGY

MEDICAL COLLEGE AND HOSPITAL, KOLKATA,

"LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

Case serial no:

OPD ticket no: **Date:**

Name: **Age:** **Sex: M/F**

Education; **marital status:**

Husband's name:

Religion: H/M/C/others **Occupation:**

Ph. No. :

Address:

HISTORY:

Presenting complains: dysmenorrheal, heavy/irregular bleeding, pelvic pain. Lower abdominal/back pain, dyspareunia,dyschezia, bloating, nausea/vomiting, pain on micturition/ urinary frequency

Duration: yrs/months/

MENSTRUAL HISTORY:

Menarche:

Duration: **cycle:**

OBSTETRIC HISTORY:

Parity in detail :

Previous h/o child birth/abortion/ectopic:

Last Menstrual Period

PAST HISTORY: Systemic ds: jaundice/chronic liver disease ds/Liver adenoma or carcinoma/DM/S.HTN/TB/CVA/Severe migraine

h/o recurrent UTI

Family history: of similar ds – yes/ no

h/o DM/S.HTN/CVA

If yes, details:

Drug history: for present/any past condition

Personal history: addiction:

Food habits: veg/non-veg:

Any other relevant history:

EXAMINATION

General survey:

height: **weight:**

Pallor: icterus: edema: clubbing:

Pulse rate: **BP:**

Systemic examination:

Abdominal examination

Pelvic examination

Speculum examination

Rectal or rectovaginal examination

INVESTIGATIONS:

Baseline investigation:

CBC

LFT

RBS,S.Urea, Creatinine, Sodium, Potassium

USG/Laparoscopy whichever is feasible

TREATMENT PRESCRIBED:

Date :	

Complication as a result of treatment:

Date:	Letrozole	Dienogest

PATIENT CONSENT FORM

NAME OF THE STUDY: "LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

I.....S/D/W of..... resident of.....aged…….years, I do here by declare that I am voluntarily giving my consent to participate in the study entitled: AN OBSERVATIONAL,COMPARITIVE STUDY BETWEEN LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

I have been explained to my full satisfaction in my own language about the procedure involved in the study along with right to refuse to participate in the study at any time during course of the study. This refusal however is not going to affect the treat ment of my illness from the department.

I have been assured that my medical records will be kept confidential and will not be used without my permission.

I do hereby declare that I will provide medical history of the disease, undergo clinical examination, and allow collection of necessary clinical material.

I have also been informed to contact Dr.Swadha Pandey, PGT for M.S in Department of Obstetrics and Gynaecology, Medical College Kolkata (Mob no. 7908851587)n case of any emergency arising during the study.

Name of the declarant/guardian (in case of minor)…….....

Signature of the declarant/guardian (in case of minor)…….....

Date……. Place: Kolkata

Name of the witness…….....

Signature of the witness…….....

Date…… Place: Kolkata

Name of the investigator: ……..…..

Signature of the investigator…….....

Date…… Place: Kolkata

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DR.Swadha Pandey (7908851587) MS PGT (obs&gynae) ,Medical College, Kolkata–□□ □□□□□□□□ □□□□□ □□□□□□ □□□□ □□□□□□□

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INFORMATION SHEET

I Mr/ Mrs/ _____ by exercising power of free choice, hereby give my consent to be included as a subject in the study LETROZOLE VERSUS DIENOGEST IN MANAGEMENT OF PAIN IN PELVIC ENDOMETRIOSIS"

I have been informed to my satisfaction by the principle investigator the purpose of the study, and the study will be published in any journal or in presentation which will be used in medical education or may be seen by any non-doctors.

I have been informed and I am aware that for the above-mentioned study my photograph will be taken if needed, hiding the face to maintain anonymity and confidentiality. Photographs of my reports will also be taken and will be used in this study.

I have been informed that all my information will be published without my name and every attempt will be maintained to ensure anonymity. I understand, however, that complete anonymity cannot be guaranteed and it is possible that somewhere somebody may identify me.

I am also aware of my right to opt out of the study at any time during the course of study without having to give the reason to do so.

I agree to adhere to doctors' information and co-operate fully.

Patient's name: _____

Patient's signature: _____ Date: _____

Name of the Principle Investigator:

DR. Swadha Pandey Junior resident

Department of Obstetrics & Gynaecology

Medical College, Kolkata.

Contact number-+91-7908851587

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তথ্য ফর্ম

আমি □□□/ □□□□□,/ □□□,"_____". পছন্দ ক্ষমতা অনুশীলন করে, অধ্যয়নের একটি বিষয় হিসাবে অন্তর্ভুক্ত করার জন্য আমার সম্মতি দিলাম " □□□□□□ □□□□□□□□□□□□□□□□ □□□□□□ □□□□□□□□□□□□□ □□□□□□□□□□ □□□□ □□□□□□□□□□"

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□মাকে অবহিত করা হয়েছে এবং আমি সচেতন যে উপরে উল্লিখিত অধ্যয়নের জন্য আমার ছবি প্রয়োজন হলে নেওয়া হবে, নামহীনতা এবং গোপনীয়তা বজায় রাখার জন্য মুখ লুকিয়ে রাখা হবে। আমার প্রতিবেদনের ছবিও তোলা হবে এবং এই গবেষণায় ব্যবহার করা হবে।

আমাকে জানানো হয়েছে যে আমার সমস্ত তথ্য আমার নাম ছাড়াই প্রকাশিত হবে এবং নামহীনতা নিশ্চিত করার জন্য প্রতিটি প্রচেষ্টা বজায় রাখা হবে। যাইহোক, আমি বুঝতে পারি যে সম্পূর্ণ নামহীনতা নিশ্চিত করা যায় না এবং এটি সম্ভব যে কোথাও কেউ আমাকে সনাক্ত করতে পারে।

আমি অধ্যয়নের সময় যে কোনও সময় অধ্যয়ন থেকে বেরিয়ে আসার অধিকার সম্পর্কেও সচেতন, এটি করার কারণ না দিয়ে।

আমি ডাক্তারদের তথ্য মেনে চলতে এবং সম্পূর্ণরূপে সহযোগিতা করতে সম্মত।

রোগীর নাম: _____

রোগীর স্বাক্ষর: _____ তারিখ _____

মূল তদন্তকারীর নাম:

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