Communication of decisions of the 107th Institutional Ethics Committee

IEC code: 2018-207-EMP-107
Agenda Item No. 16

Title of project: Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of Pharmacological intervention to improve sleep on these parameters

Principal Investigator: Dr U C Ghosal
Department: Gastroenterology
Name and Address of Institution: Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, 226014
New/Re-review project: New

Date, time and venue of meeting: 19-Jan-19 11.00 AM at Committee room of Guest house SGPGI

Dear Dr,
Institutional Ethics Committee reviewed and discussed your application to conduct the research study during the IEC meeting held on 19-Jan-19.

List of documents reviewed:
1. Project Submission Form
2. Study Protocol
3. Case Report Form
4. Consent of Head of the PI's Department
5. Research Committee/Department committee /Doctoral Committee/Scientific Committee Approval
6. Undertaking by the PI
7. Conflict of Interest Statement by PI
8. CV of investigator outside SGPGI or of the student
9. Participant Information document (PID) consent forms CF) in English and Hindi
Communication of decisions of the 107th Institutional Ethics Committee

IEC code: 2018-207-EMP-107  
PGI/BE/244/2018

Agenda Item No. 16  
Date: 09-May-19

The following members of the Institutional Ethics committee (IEC) were present at the meeting held on 19-Jan-19
Dr Chandishwar Nath Retd Chief Scientist CSIR-CDRI Lucknow - Chairman (Officiating)
Prof S.K Misra, Dean SGPGI - Member
Justice Vishnu Sahai Former Chief Justice Allahabad High Court - Member
Shri Vijay Varma, Chairman Upbhokta Forum Lucknow - Member
Shri Sharat Pradhan Senior Journalist Lucknow - Member
Prof Manish Kumar Verma Deptt of Sociology BBAU, Lucknow - Member
Dr. Mohan Gurjar, Deptt. Of CCM, SGPGI, Lucknow - Member
Prof. Vinita Agrawal, Deptt. Of Pathology, SGPGI, Lucknow - Member Secretary

IEC has taken following decisions for the study/trial:

Scientific issues, ethical issues and PID, CF were discussed.
The committee has given the following suggestions to the PI:
1. If the drug ‘Melatonin’ is indicated and approved for therapy, what is the beneficial outcome of this study?
2. Justify the use of placebo?
3. Mention the side-effects of the drug. Mention the provision of support and medical treatment for study related adverse side-effects.
4. The study involves ‘evaluation of sleep abnormalities’. Include a psychiatrist in the study.
5. Mention source of healthy controls.
7. The study will require CTRI registration before start of study.
8. Submit properly framed separate PID’s for controls, patients and legally accepted relative (LAR). Mention the collection of blood and stool also in the PID.
9. The departmental research committee meeting on 2/1/2019, however, the meeting minutes
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signed on 30/12/2018. Clarify.

Decision Major Modification. Kindly resubmit revised protocol and other documents.

Pl advised to submit above correction within 4 weeks, failing which the project will not be considered in next IEC meeting for ethical approval.

As per above recommendations of IEC, the project/trial with documents has been placed for the reviewed by the following 3-members committee.

1. Dr. Chandishwar Nath, Member Scientist G and Chief Scientist, Division of Toxicology, CDRI, Lucknow
2. Dr. Vinita Das Dept. of Obst. And Gynae, KGMU, Lucknow
3. Dr.Vinita Agrawal, Prof, Dept of Pathology, SGPGIMS, Lucknow

The 3-members has gone through the required documents suggested by IEC and following decision has been taken,

'Decision:Approved.'

The approval is valid until one year or duration of project whichever is later from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of annual status report.

Following points must be noted:

1.IEC should be informed of the date of commencement of study (AN5-V2/SGSOP 06/V3) and annual progress.
2.PI and other investigators should co-operate with IEC, which may monitor the trial from time to time.
3.The decision was arrived at through consensus. Neither PI nor any of proposed study team members was present during the decision making of the IEC.
4.At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD and getting IEC concurrence and submitting status report, including accounts details should be submitted to HOD, IEC and extramural sponsors.
5.The IEC functions in accordance with the GCP-CDSCO/ICMR/Schedule Y guidelines/ICH-GCP.
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6. New information or any SAE, which could affect any study, must be communicated to IEC and sponsors. The PI should report SAEs occurred for IEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the Bioethics cell should receive the SAE reporting form within 24 hours of the occurrence.

7. In the events of any protocol amendments, IEC must be informed and the amendments should be highlighted in clear terms.

8. Any deviation/violation/waiver in the protocol must be informed to the IEC as detailed in AN1-V3/SGSOP 09/V3.

9. If project/drug/device trial initiation not done in next 6 months from date of approval from IEC, further extension will not be granted and it will require resubmission to IEC.

We hereby confirm that the Institutional Ethics Committee is organized and operates as per amended schedule Y (20th Jan 2005), ICH GCP guidelines and applicable regulations.

Thanking You,
Your Sincerely,

(Dr. Vinita Agrawal)
Member Secretary
IEC, SGPGI, Lucknow.
AN1-V1/SGSOP 03/V1

Project Submission Form for Review by IEC
(6 copies and a CD required)

A. Identification details:

*IEC Code No. (To be filled by the Bioethics cell):

Study/Protocol No. (For drug/device trials/any other, to be filled by PI):

<table>
<thead>
<tr>
<th>Type of project</th>
<th>Intramural [ ]</th>
<th>Extramural [ ]</th>
<th>Drug trial/device [ ]</th>
<th>Independent [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD/DM/MCh/PhD/SRF Project [ ]</td>
<td>Collaborative [ ]</td>
<td>Other [ ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Status of review: New [ ] Revised [ ]

Proposal Title: Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters

B. Investigator details:

<table>
<thead>
<tr>
<th><strong>PI</strong></th>
<th>Name, Designation, Qualifications</th>
<th>Departmental Tel Nos. &amp; Email ID</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Uday Chand Ghoshal, DM Professor Gastroenterology SGPGI</td>
<td>CUG:8004904780 Ext (O) 4405 (R) 4406 Email: <a href="mailto:udayghoshal@gmail.com">udayghoshal@gmail.com</a></td>
<td></td>
<td>uCgmG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.Co-PI</th>
<th>Name, Designation, Qualifications</th>
<th>Departmental Tel Nos. &amp; Email ID</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ujjala Ghoshal, Professor, Microbiology SGPGI</td>
<td>CUG:8004904513 Ext(O) 5221 (R) 4406 Email: <a href="mailto:ujjalaghoshal@yahoo.co.in">ujjalaghoshal@yahoo.co.in</a></td>
<td></td>
<td>ujgho</td>
</tr>
</tbody>
</table>

**One page recent, signed and dated curriculum vitae of the investigators indicating qualifications and relevant experience for new or investigator outside SGPGI or of the student (MD/MS/DM/MCh/PhD) who has submitted thesis/project**
C. Sponsor Information:  Applicable [✓]  Not applicable []

1. Name of sponsor/CRO: Will be submitted to UP CST for funding after Ethics clearance

2. Indian:  a) Government [ ]  Central [ ]  State [✓]  Institutional [ ]
   b) Private []

3. International: Government [✓]  Private []  UN Agencies [ ]

4. Industry: National [ ]  Multinational [ ]

5. Contact address of sponsor/CRO: Not applicable

6. Budget: Rs. Provided in the project

7. Details of allocation of budget in Clinical Trial Agreement: Yes [ ]  No [ ] Not applicable

D. Study related Information:

1. Design of study: Epidemiological [ ]  Basic Sciences [ ]  Behavioral [ ]
   Clinical [✓]  Interventional [ ]  Single Centre [ ]  Multicentre [ ]

2. No. of participants:  SGPGI  Total (if multicentre)
   Patient*  97  97
   Control*  97  97

3. Duration of study: Two years

4. Duration of subject participation (no. of visit by a participant in study): Two
   *Please mention sample size calculation and source of control in methodology

The related case-control studies were reviewed for calculation of sample size. The frequency of sleep disorder among IBS was observed to be 35% and 43% whereas in control it has been observed to be 29 and 14% respectively. Taking the average of these, we considered among IBS case and controls the average frequency of sleep disorder is 40% and 22%, respectively, considering a power of 80%, alpha value of 0.05 and ratio of case to control is 1:1. As per the
calculation, we propose to include 97 cases and 97 controls.

For interventional study with melatonin and placebo, sample size was calculated based on the data that improvement occurred in 88% patients if treated with melatonin as compared to 47% with placebo (Lu WZ. APT 2005; 22: 927-934). Hence, 34 patients will be treated with melatonin and 34 with placebo (two sided CI 99%, power 80%, case:control 1:1, and p value <0.05). Considering 20-25% loss to follow-up, 97 patients with IBS will be randomized to melatonin and placebo.
E. Interventional study:  Yes [✔]  No [ ]  If No, move to next section i.e. NA

1. Does the study involve use of
   - Drugs □
   - Devices □
   - Vaccines □
   - Radiopharmaceutical □
   - Recombinant DNA/Gene therapy □
   - Stem cell □
   - (need BARC approval)
   - (need DBT- GEAC approval)
   - (NAC-SCRT registration and approval)
   - Indian Systems of Medicines/ Alternate systems of Medicine □
   - Any Other □  None □

2. Is it approved and marketed
   - In India □
   - UK & Europe □
   - USA □
   - Other Countries, Specify ________

3. Does it involve a change in use, dosage, route of administration?  Yes □  No □
   If yes, whether DCGI’s/Any other Regulatory Authority’s Permission is obtained?
     Yes □  No □
     Yes □  No □
     Yes □  No □

4. Is it an Investigational New Drug?  Yes □  No □
   If yes
   a. Investigator’s Brochure enclosed  Yes □  No □
   b. Preclinical studies data available (If yes, provide summary)  Yes □  No □
   c. Clinical studies data available (If yes, provide summary)  Yes □  No □
   d. Clinical study is  Phase I □  Phase II □  Phase III □  Phase IV □  NA □
     If phase I-III will the drug/device be provided free?  Yes □  No □
     If phase IV will the drug/device be provided at cost less than Hospital pharmacy?
     Yes □  No □
   e. DCGI’s permission obtained  Yes □  No □
   If yes, copy of letter enclosed  Yes □  No □

5. Data monitoring
   a. Is there a plan for reporting of adverse events?  Yes ✔ □  No □
     If yes, reporting will be done to
     - Sponsor □
     - IEC ✔ □
     - Yes ✔ □  No □
   b. Is there a plan for interim analysis of data?

6. Provision for travel/treatment due to injury out of study  Yes ✔ □  No □
If yes, by Sponsor □ Investigator □ Insurance Company □ Any Other □

7. Registered with Clinical Trial Registry – India
   - Yes □ No □
   - If yes copy of certificate enclosed Will be done after Ethics clearance
     - Yes □ No □

F. Details of participant of study:

| 1. Will subjects from both sexes be recruited: | Yes [ □ ] No [ ] |
| 2. Inclusion/exclusion criteria given:        | Yes □ No [ ] |
| 3. Type of subjects:                         | Volunteers [ □ ] Patients [ □ ] |
| 4. Vulnerable subjects                       | Yes [ ] No [ □ ] |
| (if Yes tick the appropriate boxes)          | Pregnant Women [ ] Children [ ] Elderly [ ] Fetus [ ] |
|                                               | Illiterate [ ] Handicapped [ ] Terminally ill [ ] Seriously ill [ ] |
|                                               | Mentally challenged [ ] Economically & socially backward [ ] Any other [ ] |

5. Special group subjects:
   - Yes [ ] No [ □ ]
   - (if Yes tick the appropriate boxes)
     - Captives [ ] Institutionalized [ ] Employees [ ] Students [ ]
     - Nurses/Dependent [ ] Staff [ ] Armed Forces [ ] Any Other [ ]

G. Privacy and confidentiality:

| 1. Study Involves                               | Direct Identifiers (Pt. identified by name/Cr. no.) □ |
|                                               | Indirect Identifiers/Coded (Pt. identified after break of code) √ □ |
|                                               | Completely Anonymised /Delinked (Pt. cannot identified) □ |
| 2. Confidential handling of data by staff     | Yes □ No □ |
H. Detail of sample collection (If no sample being collected, move to next section i.e. I):

A. Regarding sample collection

1. Collection of organs or body fluids or blood. If yes, please specify
   - Yes □ No □
   - Type: Blood, urine, stool
   - Amount each time \( \text{urine} \) 5 ml
   - Total \( \text{urine} \) 5 ml
   - No. of time two

2. Collection of fetal tissue or abortus. If yes, please specify
   - Yes □ No □

3. Use of pre-existing/stored/left over samples. If yes, please specify
   - Yes □ No □

4. Proper disposal of material
   - Yes □ No □

B. Special situation

1. Will any sample collected from the patients be sent abroad?
   - Yes □ No □
   - If yes, give details and address of collaborators

a. Sample will be sent abroad because (Tick appropriate box)
   - Facility not available in India □
   - Facility in India inaccessible □
   - Facility available but not being accessed □
   - If so, reasons

b. Has necessary clearance been obtained
   - Yes □ No □

2. Collection for banking/future research
   - Yes □ No □
## Participant Information Document (PID) and Consent Form:

<table>
<thead>
<tr>
<th>1. Consent</th>
<th>*Written ☑</th>
<th>Oral ☐</th>
<th>Audio-Visual ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Information documents and consent form attached: (Tick the included elements)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Understandable language ☑</td>
<td>Alternatives to participation ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement that study involves research ☑</td>
<td>Confidentiality of records ☑</td>
<td></td>
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<tr>
<td>Sponsor of study ☑</td>
<td>Contact information ☐</td>
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<tr>
<td>Purpose and procedures ☑</td>
<td>Statement that consent is voluntary ☑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risks &amp; discomforts ☑</td>
<td>Right to withdraw ☑</td>
<td></td>
<td></td>
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<tr>
<td>Benefits ☑</td>
<td>Benefits if any on future ☑</td>
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</table>

Consent for future use of material biological ☐ NA
Free supply of drug till it is not marketed in country if necessary ☐ NA
Compensation for study related injury ☑
Translation of Participant Information Document (PID) in local Language ☐

2. If healthy volunteers, PID for them Yes ☑
3. If participant is child, PID for parent Yes ☐ NA
4. PID and Assent Form for child 8-18 yrs Yes ☐ NA
5. Consent form in English ☑ Local Languages ☑
   (For participant/healthy volunteer)
6. Who will obtain consent? PI-Co-PI ☑ Nurse/Counselor ☑
   Research Staff ☐ Any Other ☐
*If written consent is not obtained, give reasons
NA.........................................................

J. Will any advertising be done for recruitment of Subjects? Yes ☐ No ☑
   (Posters, flyers, brochure, websites – if so attach a copy)

K. For archival of record by Bioethics cell for more than 5 years required
   Yes ☑ No ☐ Not applicable ☐
   If yes, for how many years.........................

L.
**Risk and benefits:**

1. **Is there physical/social/psychological risk/discomfort?**
   - Yes ☑ No ☐
   - If yes, Minimal or no risk ☐
   - More than minimum risk ☐
   - High risk ☐

2. **Is there benefit**
   - a) to the subject?
     - Direct ☑
     - Indirect ☐
   - b) to the society
   - Yes ☑ No ☐

3. **Do you think that the risk is in commensurate with the benefits to be accrued subjects/community/country?**
   - Yes ☑ No ☐

4. **Please identify the ethical issues involved in your study:** There is no ethical issue involved in our study.

**M. Do you have conflict of interest?**
- Yes ☐ No ☑
  (Financial/Non financial)
- If yes, specify __________________________
Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters

Investigators

Uday C Ghoshal, Prof. Dept. of Gastroenterology, SGPGI, Lucknow

Ujjala Ghoshal, Prof. Dept. of Microbiology, SGPGI, Lucknow

Brief proposal summary:

Irritable bowel syndrome (IBS), a common gastrointestinal (GI) disorder in India and in the rest of the World, is enigmatic in its pathogenesis. IBS is associated with recurrent abdominal pain or discomfort, bloating, incomplete evacuation, altered bowel habit, and abnormal stool forms (1, 2). The etiology of IBS remains unclear and different factors were thought to be involved like, genetics and environmental factors, visceral hypersensitivity, altered gut microbiota or disorder of the microbiota-gut-brain axis and various psychological factors like anxiety, depression, and insomnia or sleep disturbance (3). Due to increasing work pressure in today’s society, and the consequent shift duty and psychological stress, the frequency of sleep disorders is increasing; disturbed sleep may be associated with a vicious cycle in which altered sleep may result in gastrointestinal (GI) disturbances, which in turn, may jeopardize sleep further. Disorder of the gut microbiota, the largest organ of the human body, is being suggested to be responsible for several GI and extra-GI diseases. Qualitative change in gut microbiota is currently studied by next generation sequencing. Gut and sleep patterns work in an axis - a two-way street of communication, some studies reported altered gut microbiota or dysbiosis modulates peripheral
and central nervous system function, leading to alterations in brain signaling and behavior that possibly leads to sleep disturbances (4).

Several case control and meta-analyses have reported an association between sleep disturbance and irritable bowel syndrome (IBS) as compared to healthy controls. However, the data regarding relationship between sleep disturbance and severity parameters of IBS have not been widely reported; moreover, interventions that improve disturbed sleep on these parameters are scanty. There is no systematic study on sleep disorders among patients with IBS from India.

Melatonin is a hormone made by the pineal gland; its biosynthesis is initiated by the uptake of the essential amino acid tryptophan and is an important inducer of sleep. Abnormality in melatonin has been shown in several studies on patients of IBS and functional constipation. A few studies also reported improvement in sleep and GI function after administration of melatonin. However, these studies had limitations due to small sample size, lack of randomization and inclusion of patients without sleep disorder. Moreover, there is no study from India on this issue (5,6,7).

Accordingly, we wish to undertake a study with the following aims:

(i) Quality of sleep among patients with IBS and healthy controls.

(ii) Levels of 6-Hydroxymelatonin sulphate (metabolite of melatonin) both in patients with IBS and healthy controls.

(iii) Relationship between the IBS symptom severity (IBS-SSS), Health-Related Quality of Life (HRQL) and sleep disorder and melatonin deficiency,

(iv) Relationship between gut dysbiosis and the above parameters

(v) Effect of melatonin administration on IBS symptoms, HRQL and sleep.
Since sleep disturbance may be an important issue in IBS, the patients with IBS will be treated both with melatonin and standard treatment. Parameters like IBS-SSS, HRQL (8), Hospital Anxiety and Depression Scale (HADS) score (9), Pittsburgh Sleep Quality Index (PSQI) (10) will be studied in patients with IBS and healthy controls and these parameters would be repeated after 1 and 3 months follow-up in patients only. Urinary 6-Hydroxymelatonin sulphate will be studied in patients and controls before treatment with melatonin and it will be repeated after one month among patients with IBS only. Sleep study will be performed by PSQI questionnaire and also by polysomnography depending on the availability of the instrument. Study will analyse the effect of melatonin in GI and sleep disorder functions. Data will be analyzed using appropriate statistical techniques. P-values lesser than 0.05 will be considered significant.

**Study protocol:**

**Sample size:**

The related case-control studies were reviewed for calculation of sample size. The frequency of sleep disorder among IBS was observed to be 35% and 43% whereas in control it has been observed to be 29 and 14% respectively. Taking the average of these, we considered among IBS case and controls the average frequency of sleep disorder is 40% and 22%, respectively, considering a power of 80%, alpha value of 0.05 and ratio of case to control is 1:1. As per the calculation, we propose to include 97 cases and 97 controls.

For interventional study with melatonin and placebo, sample size was calculated based on the data that improvement occurred in 88% patients if treated with melatonin as compared to 47% with placebo (Lu WZ. APT 2005; 22: 927-934). Hence, 34 patients will be treated with melatonin and 34 with placebo (two sided CI 99%, power 80%, case:control 1:1, and p value
<0.05). Considering 20-25% loss to follow-up, 97 patients with IBS will be randomized to melatonin and placebo.

**Inclusion criteria**

- Diagnosis by ROME III/IV criteria.
- Willing to participate and informed consent is obtained.

**Exclusion criteria**

- Presence of alarm symptoms such as severe organic GI diseases, unexplained iron deficiency anaemia, unintentional weight loss, palpable abdominal mass.
- No active substance intake.
Fund Requirements:

Detailed year wise breakup under the heading of staff, Equipment, Contingencies etc. (List of the items/compounds may be given)

Amount of grant proposed: (in Rs.)

<table>
<thead>
<tr>
<th></th>
<th>1st year</th>
<th>2nd year</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff</td>
<td>2,40,000</td>
<td>2,40,000</td>
<td>4,80,000</td>
</tr>
<tr>
<td>Junior Research Assistant (JRA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contingencies</td>
<td>5,50,000</td>
<td>2,70,000</td>
<td>5,32,000</td>
</tr>
<tr>
<td>Equipments</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Grand total</td>
<td>7,90,000</td>
<td>5,10,000</td>
<td>13,00,000</td>
</tr>
</tbody>
</table>

Contingencies:

DNA extraction kits, Oligonucleotide primers, SYBR® Green master mix, Melatonin-Sulfate Urine ELISA kit, other lab reagents and glassware, ladder, Agarose, Taq polymerase, dNTPs, PCR tubes, Microtips, pipettes, gut microbiota next-generation sequencing.
References

1. Ghoshal UC, Shukla A. Malnutrition in inflammatory bowel disease patients in northern India: frequency and factors influencing its development.


Flowchart:

Frequency of sleep abnormalities in patients IBS and healthy controls

IBS patients (n=97)

- IBS Questionnaire
- IBS symptom severity
- HRQL
- Pittsburgh sleep quality
- HADS
- 6-OHM levels in urine
- Gut microbiota study in a subset

Study

Randomized

Melatonin + Standard Rx

Placebo + Standard Rx

After one and three month follow-up

IBS Questionnaire
IBS symptom severity
HRQL
Pittsburgh sleep quality
HADS
6-OHM levels in urine

Repeat study

Statistical Evaluation

Healthy groups (n=97)

Study

No treatment

- HRQL
- Pittsburgh sleep quality
- HADS
- 6-OHM levels in urine
- Gut microbiota study in a subset
**Brief proposal summary**

Aim(s) and objectives, methodology describing the potential risks and benefits, outcome measures (maximum 500 words).

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**Signature of PI**

**Name:** Dr Uday Chand Ghoshal  
**Date:** 30/12/18

***Please also submit detail Study/Project Protocol separately (Short review of literature, justification for study, aim, methodology, inclusion, exclusion criteria, statistical analysis).***
AN2-V1/SGSOP 03/V1

Consent of Head of the PI’s Department

Date: 30.12.2018

I have reviewed the project “Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters” submitted by Dr Uday C Ghoshal, Principal Investigator from my department. I endorse the project and have ‘no objection’ for submission for consideration by Ethics committee.

I concur with the participants / investigators included in the study.

[Signature and date]

Gastroenterology

Professor & HOD

Name

Department
Department research committee Approval

The project titled "Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters" with all the accompanying documents listed above was reviewed by the Research committee/department committee /doctoral committee/scientific committee presented on ---------------- at SGPGI. The committee has granted approval on the scientific content of the project. The proposal may now be reviewed by the Institutional Ethics Committee for granting ethical approval.

*Signature of *HOD
Date: 20/12/18

*In case of student (MD/MS/DM/MCh) or independent project/extramural
**In case of intramural
***In case of PhD or any other project
****Not applicable to sponsor/CRO initiated drug/device trials

The PI should also attach a copy of minutes of “Research committee/department committee /doctoral committee/scientific committee”.

Dr. UDAY C. GHOSELM
M.D., D.N.B., D.M., FAACG
Department of Gastroenterology
SGPGIMS, Lucknow-226015
AN4-V1/SGSOP 03/V1

Undertaking by the Principal Investigator

1. Name of the project:
   Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters

2. Name, designation and department of the principal investigator:
   Dr Uday Chand Ghoshal
   Professor
   Gastroenterology, SGPGI

3. Other members of the research team:
   Dr Ujjala Ghoshal, Microbiology, SGPGI, Lucknow

4. Name and address of any other medical college, hospital or institution where parts of the study will be done:

5. Number of ongoing projects/clinical trials in which you are PI:
   a. Number of clinical trials with active enrolments: 5
   b. Number of clinical trials with follow up only: 0
   c. Total number of ongoing projects/clinical trials (Projects+a+b): 5

1. I confirm that I will initiate the study only after obtaining all regulatory clearances.

2. I will not implement any deviation from the approved protocol without prior consent of the sponsor nature and it will be intimated to the IEC at the earliest.

3. I confirm that the Co-PI and other members of the study team have been informed about their obligations and are qualified to meet them.
4. I will personally supervise the study and ensure that requirements of obtaining informed consent and other ethical requirements under national regulatory and ICMR guidelines are adhered to.

5. I will maintain accurate and complete record of all cases in accordance with GCP provisions and make them available for audit/inspection by IEC, regulatory authorities, sponsors or their authorized representatives.

6. I will inform the IEC and the sponsors of any unexpected or serious adverse event at the earliest and definitely within seven days of its occurrence.

7. I will maintain confidentiality of the identity of all participating subjects and assure security and confidentiality of study data.

8. I and my colleagues will comply with statutory obligations, requirements and guidelines applicable to such clinical studies.

9. I will inform IEC if there is change in funding agency/status.

10. I will inform IEC of the date of starting the study within 2 weeks of initiation of the trial and submit annual progress reports and final report to Member Secretary, IEC within 4 weeks of the due date.

Signature of PI

Name_Dr Uday Chand Ghoshal

Date_ 30.1 2018
AN5-V1/SGSOP 03/V1

Conflict of Interest Declaration by PI

To,
The Member Secretary
Institutional Ethics Committee
SGPGI, Lucknow.

Project entitled: Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters

Name of PI: Dr Uday C Ghoshal, Professor, Gastroenterology, SGPGI

Conflict of Interest

[ ] I hereby declare that I have no conflict of interest in my project.

[ ] I have following conflict of interest:

Signature of PI

Name: Dr Uday C Ghoshal

Date: 30/12/2018
CV* of PI or Investigator outside SGPGI or of the Student

<table>
<thead>
<tr>
<th>Name:</th>
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<tr>
<td>Date of Birth (dd/mm/yy):</td>
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<tr>
<td>Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator):</td>
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<tr>
<td>Professional Mailing Address:</td>
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<td>(Include institution name)</td>
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<tr>
<td>Telephone (Office):</td>
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<td>Telephone (Residence):</td>
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**Academic Qualifications (Most current qualification first):**

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**Current and Previous 3 Relevant Positions Including Academic Appointments (Most current position first):**

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**Brief Summary of Relevant Clinical Research Experience:**

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<th>Date:</th>
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*Signed and dated curriculum vitae of the investigators indicating qualifications and relevant experience for new or investigator outside SGPGI or of the student (MD/MS/DM/MCh/PhD) who has submitted thesis/project*
Guidelines for Devising a Participant / Legally Acceptable Guardian Information Document (PID) in English

Kindly refer to Table 3.2 for the essential elements of an informed consent document. For example, of PID in non-interventional studies, see appendix (AP7/V3). For 'Recommended Terms for use in Informed Consent Document', see appendix (AP12/V3)

1. Study Title
   Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters

2. Invitation Paragraph
   You are being invited to take part in a research/trial study. Before you decide it is important for you to understand why the research/study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your treating physician/family doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. What is the purpose of the study?
   The purpose of the study is to find out sleep abnormalities among patient with irritable bowel syndrome and control. Relationship of this sleep abnormality with all factors like:
   (i) Quality of sleep among patients with IBS and healthy controls. (ii) Levels of 6-Hydroxymelatonin sulphate (metabolite of melatonin) both in patients with IBS and healthy controls. (iii) Relationship between the IBS symptom severity (IBS-SSS), Health-Related Quality of Life (HRQL) and sleep disorder and melatonin deficiency, (iv) Relationship between gut dysbiosis and the above parameters (v) Effect of melatonin administration on IBS symptoms, HRQL and sleep. Whether correcting the sleep abnormality by pharmacotherapy will lead to improvement of quality of life.

4. Why have I been chosen?
   There will be two sheets available
   1. Healthy volunteer sheet.
   2. Patient sheet: You have been chosen because you have been suffering from IBS and do not meet any exclusion criteria namely:
      • Presence of alarm symptoms such as severe organic GI diseases, unexplained iron deficiency anaemia, unintentional weight loss, palpable abdominal mass.
      • Not proper informed consent.
• No active substance intake.

5. **Do I have to take part?**
   It is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

6. **What will happen to me if I take part?**
   If you take part you will be given some questionnaire which you have to fill up either yourself or if you have any difficulty a research assistant will help you to fill up. In addition a blood sample 5ml will withdraw and also you will ask to give urine and stool sample. In addition you may have to undergo a sleep study which involves connecting some machine to your body and you have to sleep one night while these machines are connected to. Subsequently, you will be allocated to treatment with a drug or placebo. Drug is melatonin and then you will have to undergo repeat test.

7. **What do I have to do?**
   You have to fill up questionnaire, and you have to give sample of urine, stool, and blood. You have to do get a sleep study done and all this will be free of cost.

8. **What is the drug or procedure that is being tested?**
   Effect of melatonin on your sleep, quality of life and hospital anxiety and depression scale is being studied.

9. **What are the alternatives for diagnosis or treatment?**
   You will receive standard of care (in case of diarrhea-IBS: remosetron, constipation-IBS: Psyllium husk and, and plain-IBS: oltionium bromide and peppermint). However, you are also receiving melatonin and placebo. Alternative to melatonin is alprazolam, zolpidem and diazepam. They are not as safe sleeping medicine as melatonin.

10. **What are the side effects of taking part?**
    Melatonin is a safe medicine. However, it can cause some side effects including headache, short-term feelings of depression, daytime sleepiness, dizziness, stomach cramps, and irritability.

11. **What are the possible disadvantages and risks of taking part?**
    Melatonin is an approved drug is being used as a standard of care for patients with sleep dysfunction and as outlined above is quite free from side effects.

12. **What are the possible benefits of taking part?**
Data from this study will be used to optimize the management of IBS. This information can also be used for research for the community.

13. What if new information becomes available?
   The information's collected from this study will be helpful in clinical management of IBS.

14. What happens when the research/trial study stops?
   It will not affect your treatment. You will be continuously care for by the clinician as usual.

15. What if something goes wrong?
   Though not much wrong is expected to occur, in case some problem arises, arrangement will be made to care for this we by the team caring for you including any specific treatment, as needed.

16. Will my taking part in this study be kept confidential?
   All information collected about you during the course of the research/trial will be kept strictly confidential. Any information which leaves the hospital/clinic/laboratory will have your name and address removed so that you cannot be recognized from it. However, if needed Ethics committee may be allowed to see the records.

17. What will happen to the results of the research/trial study?
   We will look in to the data at the end of the study and form results. Even if the data is published your personal information will not be disclosed in it.

18. Who is organizing and funding the research/trial?
   The study is conducted by Department of Gastroenterology, SGPGI. The patients participating in the study will not pay anything for the study.

19. Will the drug be made available after trial is over? (new drug requires continued use, till it is marketed in India)
   The drug is already approved and available in the market as standard of care.

20. Who has reviewed the study?
   IEC and departmental research committee have reviewed the study.

21. Contact for further information
   If you had any further information about study or need to contact the study team at any time, you may contact the following:

   Thank you for participating in the study.

   Dr Uday Chand Ghoshal, DM
   Professor
   Gastroenterology
   SGPGI
   Ph:8004904780
Ext:4407

Name of the Member Secretary of Ethics Committee and address with telephone numbers.
The PID should be dated and given a version number. It should state that the participant will be given a copy of the information sheet and the signed consent form.

__________________________
Signature of PI
Name ___________ C Ghoshal _______ Date __30/12/2018____

Dr Vinita Agrawal
Member Secretary Ethics Committee.
AN8-V3/SGSOP 63/V3

Consent Form (English)

Study Title
Study Number
Subject's Full Name (with father's name)
Date of Birth/Age
Address of subject

Qualification
Occupation: Student/self-employed/service/housewife/other (please tick as appropriate)
Annual income of subjects
Name and address of nominee(s) and his relation to subject

1. I confirm that I have read and understood the information document dated _______ for the above study and have had the opportunity to ask questions.
   OR I have been explained the nature of the study by the Investigator and had the opportunity to ask questions.

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that the sponsor of the clinical trial/study, others working on the Sponsor’s behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study/trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

5. I permit the use of stored sample (tissue/blood) for future research. Yes ☐ No ☐

6. I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:
Signatory's Name ___________________________ Date ___________________________

Signature of the Investigator ___________________________ Date ___________________________
Study Investigator’s Name ___________________________

Signature of the Witness ___________________________ Date ___________________________
Name of the Witness ___________________________

Received a signed copy of Participant Information Document and Consent Form.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:
________________________________________ Date ___________________________
**AN13-V1/SGSOP 03/V1**

Checklist of Documents (6 copies and a CD of all documents listed below) 
(Non Interventional trial require documents listed in Item no. 1 to 13)

*Please give page no. to all documents (start from 1, 2, 3............40 and so on.)*

*Please provide version no. and date of each document (for drug/device trial)*

**Protocol Title:** Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters

**Principal Investigator:** Dr Uday Chand Ghoshal, Professor, Gastroenterology, SGPGI

**Type of document:** Independent project

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<th>Item No.</th>
<th>Mandatory Documents (<em>with version and date</em>)</th>
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<th>No</th>
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<td>3.</td>
<td>Study Protocol (Review of literature, aim, methodology, inclusion, exclusion criteria)</td>
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<td>9 - 17</td>
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<td>4.</td>
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<td>10.</td>
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AN14-V1/SGSOP 03/V1

IEC Document Receipt Form (to be submitted in duplicate)

Type of Submission:
- New
- Revised

Protocol Title: Frequency of sleep abnormalities in patients with irritable bowel syndrome and its relationship with symptom severity, quality of life and effect of pharmacological intervention to improve sleep on these parameters

Principal Investigator: Dr Uday Chand Ghoshal, Professor, Gastroenterology, SGPGI

Type of document: Independent project

Checklist to assess the projects before they are submitted to IEC review

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*Please provide version no. and date of each document (for drug/device trial)*

Documents submitted:

( ) Complete

( ) Incomplete; will submit on.............

Comments:

Receiver Name, Sign & Date: ________________________________
(Bioethics cell)

Project submitted by Name & sign: Dr Uday Chand Ghoshal ____________________________________________
(Project or study team member)

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