## Official Title of the study:

**Evaluation of the efficacy of probiotics in treating constipation in elderly patients with multiple chronic co-morbidities: a randomized control trial**

**NCT no: Nil**

**Date of Document:**

**22nd July 2019**

# Study Protocol

## 1. Study design

This is a randomized double-blinded clinical trial study.

## 2. Study population and subjects

### Background and selection of study centers

The study will be conducted at the outpatient clinics, medical and surgical wards in Universiti Kebangsaan Malaysia Medical Centre.

## 3. Target population

3.1 The target populations are older patients aged 60 years or above with at least 2 chronic medical illnesses (Appendix A) and who complain of constipation that persists for several weeks or longer.

3.2 These patients are those who attending the medical/surgical outpatient clinics or being admitted to the medical/surgical wards in UKM Medical Centre during the study period.

The participants will be assigned to either interventional group or control randomly and the random selection is pre-determined prior to recruitment.

## 4 Inclusion criteria.

4.1 Elderly patients aged 60 years or above and able to give consent.

4.2 Patients who complain of constipation as per Mayo's clinic definition:

"Infrequent bowel movements of fewer than three bowel movements per week or difficult passage of stools that persists for several weeks or longer". (13)

4.3 Patients who have at least 2 chronic illnesses such as Diabetes Mellitus, Hypertensions, Chronic Kidney disease, Chronic Lung disease, or any medical illness which are prone to have constipation.

**5. Exclusion criteria.**

5.1 Patients with constipation of organic cause such as colorectal carcinoma, colonic ischaemia, inflammation, post radiation stricture, obstruction or presence of external compression.

5.2 Patients with constipation of neurological causes such as cerebrovascular disease and stroke, Parkinson's disease, autonomic neuropathy and spinal cord lesions.

5.3 Patients who is taking calcium supplements more than 1500mg a day.

5.4 Patients who are immune-compromised or critically ill.

5.5 Patients who are on opioid analgesia.

5.6 Patients with psychiatric illness.

5.7 Patients who are on any form of medications at point of entering the study that altered the normal bowel movement (either decreasing or increasing the peristalsis of the gut)

5.8 Patients who refuse to enter or consent for the study.

**6. Subject withdrawal and Drop out**

Subjects will be withdrawn from the study in the event of:

1. Consent is withdrawn by the patient.
2. Patients will be withdrawn from the study if they experience intolerable or excessive side effects due to the probiotics.

Subject drop out is predicted at 10% and is taken into consideration in the sample size calculation.

**7. Study Intervention**

Patient will be randomized into a treatment or control group. No other treatments such as laxatives or enemas are given to all patients.

1. Treatment group.
    a. Each patient will receive probiotics in form of granular powdered microbial cell preparation (Hexbio®) – Specialized formulation of six microbial strains containing:
        i. Lactobacillus acidophilus BCMC® 12130
        ii. Lactobacillus casei BCMC® 12313
        iii. Lactobacillus lactis BCMC® 12451

iv. Bifidobacterium bifidum BCMC® 02290
v. Bifidobacterium infantis BCMC® 02129
vi. Bifidobacterium longum BCMC® 02120

b. Dosage: 1 sachet twice a day after meals for 1 week.

2. Control group
   a. Each patient will receive placebo sample of similar appearance and composition but do not contain probiotics.

**8. Efficacy, Safety and Other Assessments**

**8.1 Primary end point**

A completed questionnaire on patient's demographic and medical illness data, stool output/day, stool consistency per output/day and constipated related symptoms scoring/day over the period of 7 study days.

**8.2 Safety**

Patients will be counseled that generally safety profile of probiotics seems to be good. Based on the available trials, no adverse effects were noted. There might be a concern issue of safety in immune-compromised patients or those critically ill, which they will be excluded in this study.

Patients will be withdrawn from the study if they experience intolerable or any possible excessive side effects due to probiotics.

**9. Assessment variables and methods of assessing.**

9.1 Targeted patients will be assessed with a questionnaire (Appendix C) on gastrointestinal symptoms, well-being and stool habits. The stool consistency will be scored by a seven-point scale according to the Bristol Stool Form Scale (Appendix B). Severity of constipation will be categorized into four groups (severe, moderate, mild and no symptoms). Symptoms specifically

related to constipation such as bloating and flatulence will be recorded in detail. Severity of symptom is measured by Likert score of frequency (Very frequently, frequently, occasionally, rarely and never).

9.2 Each individual patient will be required to fill in the questionnaire at the beginning of the trial. Subsequently, patient will be required to fill up the stool chart and recorded their symptoms in a given dairy daily during the study period. Training on how to use and record the dairy will be conducted upon embarking into the study. A contact number will be advised to the participants to aid their understanding. The dairy will be collected at day 7 upon completion of the study.

**Other assessment**

1. Assessment of the presence of underlying medical illness will be done at the initial presentation, assessed by questionnaire about the medical history and physical examination.

**10. Study conduct**

10.1 Elderly patients attending medical/surgical clinics or being admitted to the medical/surgical wards PPUKM will be screened. Those with underlying medical illnesses and suspected to have constipation are selected. Random selection of the participants either for intervention group or control will be pre-determining during screening.

10.2 A written consent is obtained. ( Appendix E)

10.3 The patients' demographic data and medical history will be obtained by conducting an interview and a physical examination.

10.4 In the first interview, patient will also be asked to complete a questionnaire on the gastrointestinal symptoms, stool consistency and severity of constipation.

Patients will be given 7 days' supply of placebo or probiotics, which patient are required to take each sachet of Hexbio® or placebo twice per day for 7 days.

10.5 A training of using the daily stool dairy will be done at the beginning of study. Upon completion (day 7) the dairy will be collected and data will be analyzed.

**FLOW CHART**

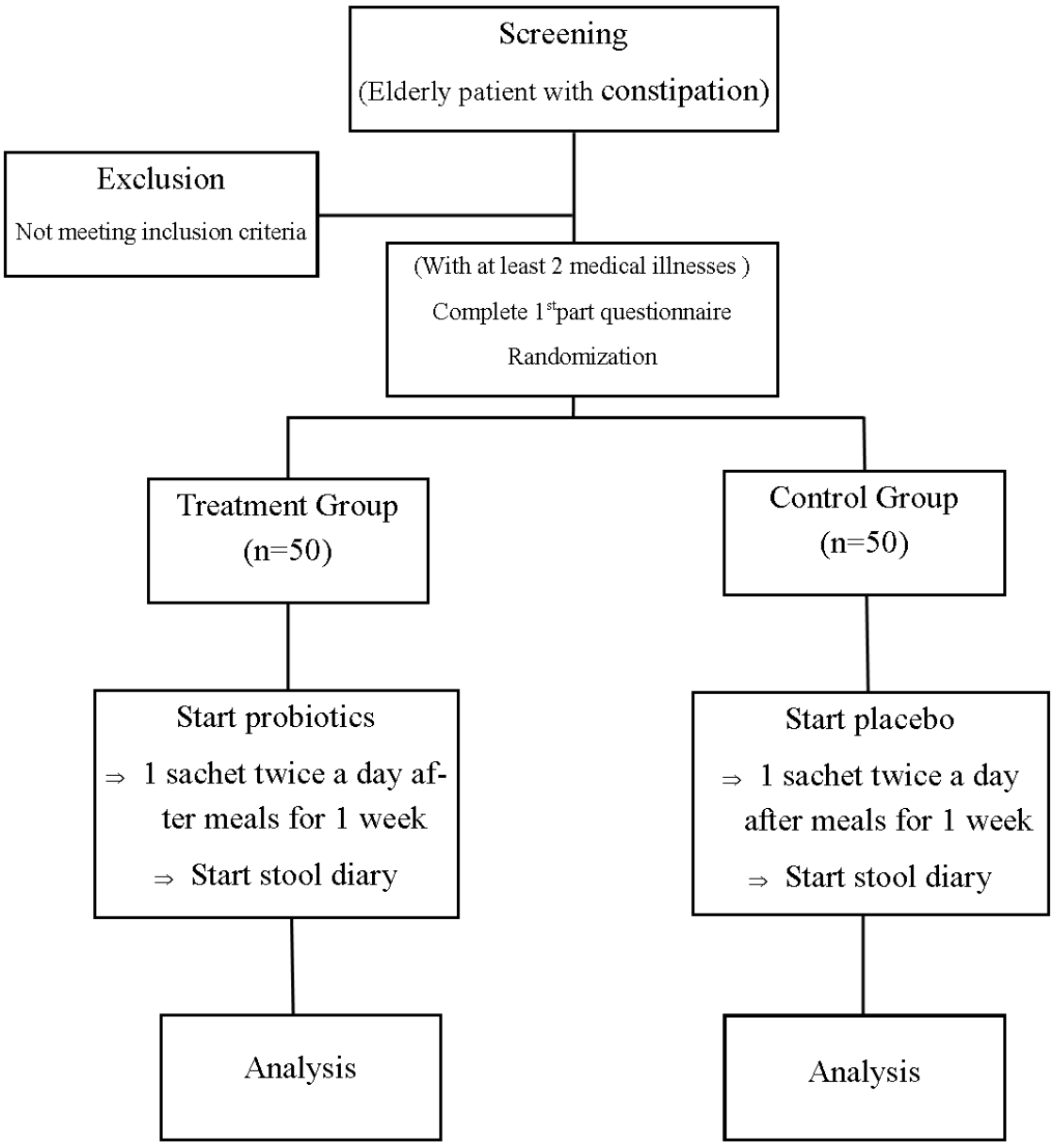



Figure 1. Flow chart of the study methodology.

GLOSSARY OF TERMS

1. **Probiotics**

   Living microorganisms that enter the gastrointestinal tract in an active form in sufficient numbers to exert positive effect.

2. **Constipation**

   A condition in which there is difficulty in emptying the bowels, usually associated with hardened feces.

3. **Functional Constipation**

   A condition that fulfill the **Rome III criteria for functional constipation**.

   Refer to Appendix A

4. **Bristol Stool**

   A medical aid designed to classify the form of human feces into seven categories. Refer to Appendix B

5. **Advanced Chronic Illness**

   An occurring when one or more conditions become serious enough that general health and functioning decline, and treatments begin to lose their impact.

6. **Colony Forming Unit (CFU)**

   A unit used to estimate the number of viable bacteria or fungal cells in a sample.

APPENDIX A

List of medical illness associated with constipation.

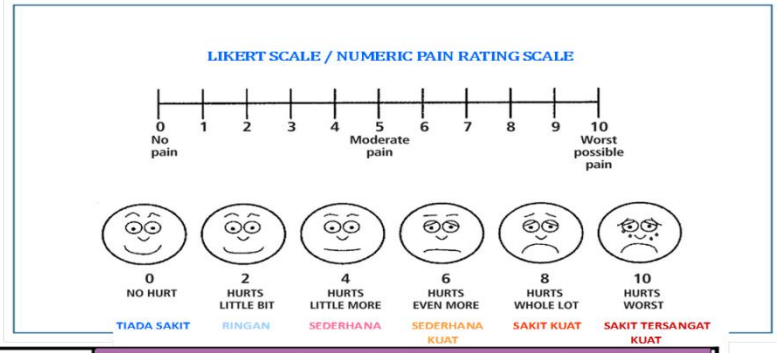
1. Diabetes Mellitus
2. Hypertension
3. Chronic Kidney disease
4. Chronic Lung disease
5. Chronic Heart Failure
6. Hypothyroidism
7. Scleroderma
8. Hyperparathyroidism
9. Uraemia
10. Hypocalcaemia
11. Hypokalaemia

APPENDIX B

## DAILY STOOL DIARY

Study No: Patient's Sticker:

**EVALUATING THE EFFECT OF PROBIOTICS IN CHRONIC CONSTIPATION ELDERLY PATIENTS WITH MULTIPLE CO-MORBIDITIES**




| DAY | CONSTIPATION RELATED SYMPTOMS | | | | | BRISTOL STOOL CHART | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | STRAINING | PAINFUL EVACUTION | BLOATING & FLATULENCE | STOMACH CRAMPS | OTHERS | TYPE 1 | TYPE 2 | TYPE 3 | TYPE 4 | TYPE 5 | TYPE 6 | TYPE 7 |
| BEFORE | | | | | | | | | | | | |
| 1 | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | |
| 6 | | | | | | | | | | | | |
| 7 | | | | | | | | | | | | |

Instructions: Please fill up the boxes according to likert scale for the constipation related symptoms and mark 'X' for the Bristol stool chart.

Bristol chart adapted from http://www.cbc.ca/stevenandchris/content/images/poop_101_1.jpg

APPENDIX C

**EVALUATING THE EFFECT OF PROBIOTICS IN CHRONIC CONSTIPATION ELDERLY PATIENTS WITH MULTIPLE CO-MORBIDITIES**

# Data Collection Form

Study Number:

Patient's Sticker:

**Socio-demography:**
Age:
Gender: Male / Female
Ethnic : Malay / Indian/ Chinese/ Others ( please state: _____)

**Clinical characteristic**
Medical illness:

| If yes, please tick: | | Durations ( years ) |
|---|---|---|
| Diabetes Mellitus | ( ) | ( ) |
| Asthma | ( ) | ( ) |
| Hypertension | ( ) | ( ) |
| Dyslipidaemia | ( ) | ( ) |
| Chronic Kidney disease | ( ) | ( ) |
| Others (please specify): _____ | | ( ) |
| _____ | | ( ) |

Symptoms associated with constipation:
(*at least in 25% of defecations – Rome III diagnostic criteria of functional constipation)

| If yes, please tick: | |
|---|---|
| Straining | ( ) |
| Lumpy or hard stools | ( ) |
| Sensation of incomplete evacuation | ( ) |
| Sensation of anorectal obstruction/ blockage | ( ) |
| Manual maneuvers to facilitate defecations | ( ) |
| Fewer than 3 defecations per week | ( ) |

Duration: _____months/ years

| Previous treatment: | | frequency: |
|---|---|---|
| Laxatives | ( ) | ( ) days/months/years |
| Probiotics | ( ) | ( ) days/months/years |
| High fibre diets | ( ) | ( ) days/months/years |
| Enemas | ( ) | ( ) days/months/years |

APPENDIX D

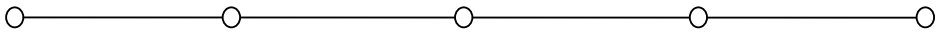
**EVALUATING THE EFFECT OF PROBIOTICS IN CHRONIC CONSTIPATION ELDERLY PATIENTS WITH MULTIPLE CO-MORBIDITIES**

## QUESTIONNAIRES

Study Number:

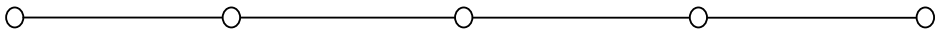
Patient's Sticker:

1. How frequent is your bowel movements per week?



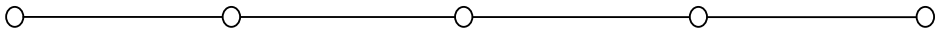
| 1-2 times per 1-2 days | 2 times per week | once per week | less than once per week | less than once per months |
|---|---|---|---|---|

2. Do you need assistance in evacuation? (enema/digital-manual maneuvers)



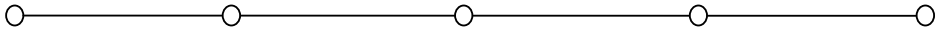
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

3. Do you have sensation of anorectal obstruction/ blockage?



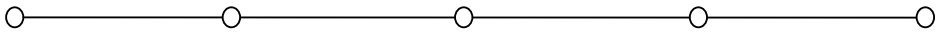
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

4. Feeling of incomplete evacuation?



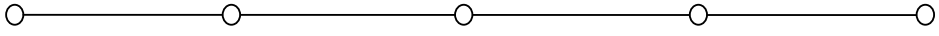
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

5. Do you have lumpy or hard stools?



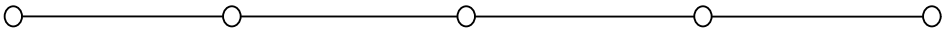
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

6. Any straining or squeezing on defecation attempts?



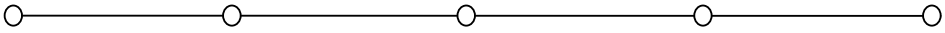
| Never | 1-3 | 3-6 | 6-9 | More than 9 |
|---|---|---|---|---|

1. How long have you had constipation?



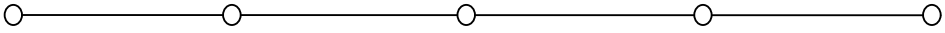
| Less than 6months | 6-12 months | 1-2 years | 3-5 years | More than 5 years |
|---|---|---|---|---|

2. Do you have bloating in your stomach?



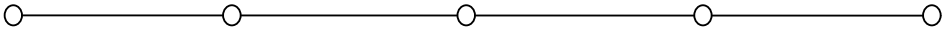
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

3. Do you have flatulence?



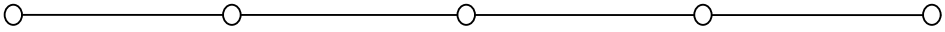
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

4. Do you have stomach cramps?



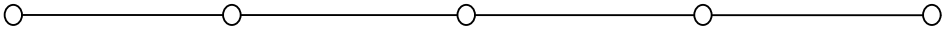
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

5. How many unsuccessful attempts of evacuation within 24hours?



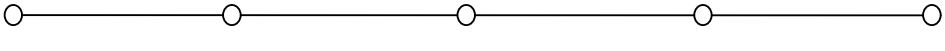
| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

6. Do you have abdominal pain?



| Never | Rarely | Occasionally | Frequently | Very frequently |
|---|---|---|---|---|

7. How long do you spend in the lavatory per attempt? (minutes)



| Less than 5 | 5-10 | 10-20 | 20-30 | More than 30 |
|---|---|---|---|---|

**Statistical analysis Plan**

The collected data was analysed using IBM SPSS Statistics for Windows version 21.0 software (IBM Corp., Armonk, NY, USA) and Microsoft Office Excel 2010software (Microsoft, Redmond, WA, USA). Statistical significance was set at $p = <0.050$.

All of the data was assessed for normality via the usual processes.

The baseline characteristic differences between the two groups were evaluated using the Mann-Whitney U and chi-squared tests. The median results of the improvement in stool frequencies and stool consistency between the treatment and placebo group were compared using the Mann-Whitney U test. The constipation-related symptom improvements were analysed using the chi-squared test.

Intention to treat analysis was used in this trial, where only the final results within the group which they were randomized, receiving the treatment and completed the treatment assignment were analysed. Participants who deviates from the protocol as being non-compliance or withdrew consent were not included into the analysis.