Application 5: Investigation of the effects of long-term supplementation with probiotics on lower gut microflora and on IBS-D symptoms (The Pro-DIBS Study)

Important note: This is a real application which has been doctored for the purposes of training. Information has been removed from the application and the application has been anonymised. The UREC does not endorse this application as a model.

The application, shown on the following pages, was discussed at the workshop. A summary of the key points raised by the participants, the UREC and the original ethics reviewers follows (this is not an exhaustive list):

- Inconsistent information has been supplied in the application form and in the email text. In the application form it says sampling every 3 weeks – in the email it says every 2-3 weeks. In the application form the compensation is £200 yet in the email text it is £300. Text in the emails also refers to PROHEMI not ProDIBS;

- There was a concern that the sensitivity of the research (e.g. the potentially embarrassing nature of providing stool samples) had not been fully considered or addressed;

- The application uses language not suitable for a lay person and medical/academic terminology has not been explained;

- Greater clarity is required concerning exactly what the participants will be required to do (e.g. where will they be required to provide the stool sample – at home, in the hospital?);

- The advertisement to be used for recruitment has not been provided;

- The standard protocol for extracting DNA from the samples has not been provided (the application states this has been attached);

- The consent form should inform the volunteer of what will happen to their samples should they withdraw from the study, and also after the study is completed;

- In the information sheet, more detail should be included re timings for the meetings/interviews i.e. is “short” 15 mins or 1 hour?

- In the recruitment email from arm 1 of the study it states that only male participants are sought, but this is not mentioned or explained anywhere else in the application;

- There is no information sheet for the 2nd arm of the study;
• The application does not state who is sponsoring/funding the study. An organisation funding the research may have a particular agenda (e.g., a company making and selling probiotics); the participants should have access to this information;

• There was a discussion about whether the compensation to be offered was appropriate. It was noted that it may be more ethical not to include the amount in the email, but to state that participants would be ‘recompensed appropriately for their time’ to help avoid potential issues with coercion;

• There was a discussion about whether the stool samples being collected constituted ‘human tissue’ under the Human Tissue Act – it was noted that this depended on whether the samples would be stored or not, but that it would be essential for the researcher to identify what approvals were necessary in this regard;

• There are a number of typographical and spelling errors in the application;

• The application form completed was for undergraduate and postgraduate-taught student research, when in fact the study was a staff project.
University Research Ethics Application Form
for Undergraduate & Postgraduate-Taught Students

This form has been approved by the University Research Ethics Committee (‘U-REC’)

Who decides if ethics approval is required and, if required, who decides which ethics review procedure (e.g. University, NHS, alternative) applies? Your Supervisor decides this.

If the UERP Procedure applies, who decides if your proposed project should be classed as 'low risk' or potentially 'high risk'? Your Supervisor decides this.

Complete this form if you are an undergraduate or a postgraduate-taught student who plans to undertake a research project which will not involve the NHS but which will involve people participating in research either directly (e.g. interviews, questionnaires) and/or indirectly (e.g. people permitting access to data and/or tissue).

Documents to enclose with this form, where appropriate:
This form should be accompanied, where appropriate, by an Information Sheet/Covering Letter/Written Script which informs the prospective participants about the proposed research, and/or by a Consent Form.

Further guidance on how to apply is at: www.shef.ac.uk/researchoffice/gov_ethics_grp/ethics/form.html

Guidance on the three ethics review procedures that together comprise the University’s Ethics Review System (i.e. on the University’s procedure, the NHS procedure, the Alternative procedure) is at: www.shef.ac.uk/researchoffice/gov_ethics_grp/ethics/er/ers.html

Once you have completed this research ethics application form in full, and other documents where appropriate, check that your name, the title of your research project and the date is contained in the footer of each page.

If your Supervisor has classed the project as 'low risk':
• Email this form, together with other documents where applicable, to your Supervisor; and
• Sign and date Annex 1 of this form and provide a paper copy to your Supervisor.

Important Note for Supervisors:
Following the ethics review the Supervisor must provide the academic department’s Ethics Administrator with a copy of the ‘low risk’ research ethics application that s/he reviewed and with a copy of the ethics decision that s/he took in relation to it. The Ethics Administrator reserves the right to consult the Chair of the academic department’s Ethics Review Panel of s/he has concerns that projects classed as low risk should in fact have been classed as potentially high risk.

If your Supervisor has classed the project as potentially 'high risk':
• Email this form, together with other documents where applicable, to your department’s Ethics Administrator; and
• Ask your Supervisor to sign and date Annex 2 of this form and provide a paper copy of it to your department’s Ethics Administrator.

Ethics Administrators are listed at: www.shef.ac.uk/researchoffice/gov_ethics_grp/ethics/people.html
University Research Ethics Application Form for Undergraduate & Postgraduate-Taught Students

I confirm that I plan to inform the prospective participants about the research project by using an Information Sheet/Covering Letter/Pre-Written Script:

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I confirm that I plan to invite prospective participants to sign a consent form:

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A1. Title of research project: Investigation of the effects of long-term supplementation with probiotics on lower gut microflora and on IBS-D symptoms
The ProDIBS Study

A2. Name of Student: This project will run for 2-3 years and involve several undergraduate placement students from the XXX course and visiting undergraduates from XXX

   Department: XXXX   Email: XXXX   Tel.: XXXX

   Name of Supervisor: XXXX

A3. Proposed Project Duration:

   Start date: XXXX   End date: XXXX

A4. Mark ‘X’ in one or more of the following boxes if your research:

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A5. Briefly summarise the project’s aims, objectives and methodology?
(this must be in language comprehensible to a lay person)

There is widespread advertising, advocacy and availability of probiotic bacteria (sometimes described as good bacteria or friendly bacteria) for self-administration with suggestions that users may experience improved gut health, yet the evidence and understanding of mechanisms of action (and benefit to the general population) remains limited. A number of papers and reviews have shown, phenomenologically, that probiotics may benefit subjects with IBS in terms of symptoms, however the mechanism of action is not understood at all. A recent study by this group undertaken in Sheffield used a similar design to that proposed herein to assess the impact of a probiotic intervention on gut flora in healthy subjects. This proposal follows a similar design to assess the impact in subjects with IBS. There are two arms to the study, 1) with small numbers where large amounts of sampling will be undertaken with the aim of determining possible mechanisms of action. The second arm 2) will use a larger sample size (previously shown to yield significant results in trials of this type) with the dual aim of i) showing the intervention has a functional benefit and ii) acquiring a set of samples for validation of mechanisms identified in objective 1.

Intervention Used
A commercially available, over-the-counter preparation of probiotics (marketed as Proven™; described as LAB-4 mix in research papers) will be used for this study. Where a placebo is used this will be maltodextrin, encapsulated so as to match the intervention capsule.

Objective 1) ProDIBS-1
This study will recruit a small number of subjects (15) with a history of GP-diagnosed diarrhoea-predominant IBS (IBS-D) to a long-term (6 month) intervention with a proprietary probiotic preparation. Subjects’ stool samples will be collected every 3 weeks for a 3 month period prior to the intervention to establish baseline variation. Sampling will continue during the 6 months of intervention, and for a three month period afterwards. This will be an exploratory trial, with subjects acting as their own controls through the baseline and washout periods.

The project is a collaboration between University of Sheffield, XXXX and XXXX University. Sheffield are conducting the intervention and will undertake primary analysis of diet, stool form and faecal SCFA; XXXX will undertake primary analysis of microbiology and faecal inflammatory markers; XXXX will undertake primary analysis of bacterial metagenomics and metemetabolomics.

Samples collected at each timepoint will be:
- Stool sample
- 24hr recall questionnaire on diet
- 7 day diary on IBS symptoms
- Short questionnaire on health to establish any recent GI upset or antibiotic use.

Stool samples will be analysed / extracted upon collection as follows:
- Stool weight
- Bristol stool chart score
- Short chain fatty acids, compounds produced by bacteria though to be potent in the prevention of cancer, will be extracted using standard methods, in line with those currently used by the research group.
- Bacterial DNA will be extracted using a standard protocol (attached), which does not yield any detectable human DNA. Once extracted bacterial DNA will be stored until sample collection is complete for analysis in a collaborating laboratory.
- The metabolome (all the small biochemicals present in the stool produced by bacteria) will be extracted using a standard protocol (attached). Once extracted, metabolomes will be stored until sample collection is complete for analysis in a collaborating laboratory.
• Residual sample will be used for analysis of lipase and protease producing bacteria, using traditional microbiological approaches. Samples will also be analysed for faecal IgA and for faecal calprotectin. This will be done on fresh sample by our collaborating laboratory.

**Objective 2) ProDIBS-2**

This study will recruit subjects with a history of GP-diagnosed diarrhoea-predominant IBS (IBS-D) to a long-term (6 month) intervention with a proprietary probiotic preparation. In contrast to ProDIBS-1, this arm of the study is designed to yield data suitable for classical statistical analysis, but also to yield a larger set of samples at critical timepoints in order to facilitate validation of models generated under objective 1.

60 subjects will be recruited to a randomised, double-blinded, placebo controlled trial of the probiotic. Questionnaires will be collected every 3 weeks for a 3 month period prior to the intervention to establish baseline variation. Sampling will continue during the 6 months of intervention, and for a three month period afterwards. Questionnaires taken will be as follows:

- 24hr recall questionnaire on diet
- 7 day diary on IBS symptoms
- Short questionnaire on health to establish any recent antibiotic use.

Additionally Faecal samples will be collected on entry to the study, at he first sampling point after starting the intervention, at the last sampling point on the intervention and at the end of the washout period. Faecal samples will be extracted as described above.

**A6. What is the potential for physical and/or psychological harm / distress to participants?**

Negligible. The probiotic preparation is available over-the-counter and will be used at recommended, safe dose.

**A7. Does your research raise any issues of personal safety for you or other researchers involved in the project? (especially if taking place outside working hours or off University premises)**

We aim to recruit subjects working in the vicinity of the XXXX Hospital and therefore able to provide samples when passed. Students therefore have no need to work outside the premises. The lab has significant experience of handling and extraction of stool and appropriate facilities are in place for this.

*If yes, explain how these issues will be managed.*

Students have HepB vaccination complete and up to date prior to starting the project. Students will be trained in extraction protocols, particularly focussing on safety and disposal. The procedures have been CoSHH approved, students will receive training and be required to adhere to CoSHH.

**A8. How will the potential participants in the project be:**

i. **Identified?**

Advertisements for volunteers will be placed around the hospital access areas. A recruitment emailshot will be sent to the volunteers list and to the Faculty email list.

ii. **Approached?**

Subjects will be asked initially to approach the study lead or students via a telephone or email address.

iii. **Recruited?**
Subjects will be sent the PIS in advance of a face-to-face meeting with a researcher. The researcher will explain the study and will answer questions the subject may have. If in agreement the subject will be asked to sign and complete consent forms.

A9. Will informed consent be obtained from the participants?

YES ✗ NO

If informed consent or consent is not to be obtained please explain why.

A9.1. This question is only applicable if you are planning to obtain informed consent:
How do you plan to obtain informed consent? (i.e. the proposed process?):

Subjects will be sent the PIS in advance of a face-to-face meeting with a researcher. The researcher will explain the study and will answer questions the subject may have. If in agreement the subject will be asked to sign and complete consent forms.

A10. What measures will be put in place to ensure confidentiality of personal data, where appropriate?

Subjects will be assigned a unique identifier in the form PD-1XX or PD-2XX according to the arm of the study, where XX is a two digit number. This will be undertaken at consent and only held on the site file which will be kept in a locked filing cabinet in a locked office. Paper records regarding diet and stool measures, electronic records, and extracted samples will only ever bear the subject’s study identifier. Analysis and publication of data will not require any identification of subjects.

A11. Will financial / in kind payments (other than reasonable expenses and compensation for time) be offered to participants? (Indicate how much and on what basis this has been decided)

YES ☐ NO ✗

Subjects will be compensated for their time commitment only, which, over a 1 year study and with frequent stool sampling justifies a payment of £200

A12. Will the research involve the production of recorded media such as audio and/or video recordings?

YES ☐ NO ✗

A12.1. This question is only applicable if you are planning to produce recorded media:
How will you ensure that there is a clear agreement with participants as to how these recorded media may be stored, used and (if appropriate) destroyed?

Guidance fact-sheets on ‘Safety and Well-Being’, on ‘Consent’ and on ‘Anonymity, Confidentiality and Data Protection’ are at:
www.shef.ac.uk/researchoffice/gov_ethics_grp/ethics/factsheets.html

These three fact-sheets have been updated in the light of new findings from three Social Research Association-funded research projects, which were published in 2008, that focused on the perspective of participants regarding their experience as participants.
Annex 1

for Undergraduate & Postgraduate-Taught Students

**Student Declaration**

*(the student completes Annex 1 if the Supervisor has classed the student’s proposed research project as ‘low risk’)*

The Supervisor needs to receive an electronic copy of the form, and other documents where appropriate, plus a signed, dated paper copy of this Annex 1 ‘the Student Declaration’.

Full Research Project Title: **Investigation of the effects of long-term supplementation with probiotics on lower gut microflora and on IBS-D symptoms**

**The ProDIBS Study**

**In signing this Student Declaration I am confirming that:**

- The research ethics application form for the above-named project is accurate to the best of my knowledge and belief.
- The above-named project will abide by the University’s ‘Good Research Practice Standards’: [www.shef.ac.uk/researchoffice/gov_ethics.grp/grpstandards.html](http://www.shef.ac.uk/researchoffice/gov_ethics.grp/grpstandards.html)
- The above-named project will abide by the University’s ‘Ethics Policy for Research Involving Human Participants, Data and Tissue’: [www.shef.ac.uk/researchoffice/gov_ethics.grp/ethics/system.html](http://www.shef.ac.uk/researchoffice/gov_ethics.grp/ethics/system.html)
- Subject to the above-named project being ethically approved I undertake to adhere to any ethics conditions that may be set.
- I will inform my Supervisor of significant changes to the above-named project that have ethical consequences.
- I will inform my Supervisor if prospective participants make a complaint about the above-named project.
- I understand that personal data about me as a researcher on the research ethics application form will be held by those involved in the ethics review process (e.g. my Supervisor and the Ethics Administrator) and that this will be managed according to Data Protection Act principles.
- **I understand that this project cannot be submitted for ethics approval in more than one department, and that if I wish to appeal against the decision made, this must be done through the original department.**

Name of Supervisor: **XXXX**

Name of student: **insert name**

Signature of student: **sign here**

Date: **insert date**
Annex 2

for Undergraduate & Postgraduate-Taught Students

Supervisor Declaration

(the Supervisor completes Annex 2 if s/he has classed the student’s proposed research project as potentially ‘high risk’)

The Ethics Administrator needs to receive an electronic copy of the form, and other documents where appropriate, plus a signed, dated paper copy of this Annex 2 ‘the Supervisor Declaration’.

Full Research Project Title: Investigation of the effects of long-term supplementation with probiotics on lower gut microflora and on IBS-D symptoms
The ProDIBS Study

In signing this Supervisor Declaration I am confirming that:

- The research ethics application form for the above-named project is accurate to the best of my knowledge and belief.
- The above-named project will abide by the University’s ‘Good Research Practice Standards’: [www.shef.ac.uk/researchoffice/gov_ethics_grp/grpstandards.html](http://www.shef.ac.uk/researchoffice/gov_ethics_grp/grpstandards.html)
- The above-named project will abide by the University’s ‘Ethics Policy for Research Involving Human Participants, Data and Tissue’: [www.shef.ac.uk/researchoffice/gov_ethics_grp/ethics/system.html](http://www.shef.ac.uk/researchoffice/gov_ethics_grp/ethics/system.html)
- Subject to the above-named project being ethically approved I will undertake to ensure that the student adheres to any ethics conditions that may be set.
- The student or the Supervisor will undertake to inform the Ethics Administrator of significant changes to the above-named project that have ethical consequences.
- The student or the Supervisor will undertake to inform the Ethics Administrator if prospective participants make a complaint about the above-named project.
- I understand that personal data about the student and/or myself on the research ethics application form will be held by those involved in the ethics review process (e.g. the Ethics Administrator and/or reviewers) and that this will be managed according to Data Protection Act principles.
- I understand that this project cannot be submitted for ethics approval in more than one department, and that if I and/or the student wish to appeal against the decision made, this must be done through the original department.

Name of Supervisor: XXXX

Name of student: insert name

Signature of Supervisor: sign here

Date: insert date
Patient Information Sheet

Investigating the effects of long-term supplementation with probiotics in IBS-D sufferers through global analysis of diet, microbiota and the metabolome (ProDIBS)

You are invited to participate in the above research project. Before you decide to participate we would like you to know what the research involves and what we expect from you. We would like you to consider the information in this sheet and understand it before you decide to participate in the project. For further information or if you have any queries please feel free to contact us.

1. What is the project’s purpose?
There is increasing evidence indicating the potential health benefits of foods containing “good” bacteria (probiotics). Short-term trials of probiotics among IBS sufferers indicate that these supplements may be beneficial in improving symptoms. Most evidence, however, comes from short supplementation periods (4-8 weeks) and we currently lack evidence as to the effects of long-term supplementation. Furthermore, an understanding of the mechanism/s by which probiotics may act is also lacking. The purpose of this project, therefore, is to study the effect of long-term supplementation among IBS-D sufferers and to gain a better understanding of the mechanism/s of action of probiotics on lower gut functioning.

2. Why have I been chosen?
You have contacted us in response to an advertisement, indicating that you may be interested in joining this study and you work close to the research unit. You will be one of about 16-18 subjects asked to join this study.

3. Do I have to take part?
It is completely your decision whether or not you participate in the study. If you do choose to take part you will be asked to complete and sign a consent form. A duplicate copy will be kept by you. If at any point you wish to withdraw from the project you are free to do so and need not give any reason for doing so.

4. What will happen to me if I take part?
You will be asked to participate in the research for 12 months. During this period we will ask to meet you every two-three weeks and collect your most recent stool (poo) sample. At the same time as this, you will participate in a short dietary recall interview and complete a 7-day IBS symptom questionnaire. You will also be asked if you have taken any antibiotics since the last sample. The meetings will be at your convenience and arranged around your “normal” pattern of bowel movements. We will collect samples, alongside dietary and symptom information, for 3 months without any probiotic supplementation to establish baseline variation and then continue to collect samples in the same way during a six-month supplementation with an over-the-counter probiotic supplement taken daily. This will be followed by a further 3-month period of sample collection once the supplementation has ended to monitor the effects of stopping the probiotic supplement.

5. What do I have to do?
- Provide the samples requested regularly over the 12-month period.
- Take the given dietary supplement daily for 6 months. The supplement will be supplied to you in capsule form
- Maintain your normal diet throughout the intervention period; however you are asked to avoid consuming foods or supplements containing very high levels of probiotics or prebiotics.

6. What are the possible disadvantages and risks of taking part?
Annex 2

Although there are no known risks with any of the supplements you may experience a change in bowel habit and increased flatulence during the first few days of taking the supplement. It is advised that if you experience any discomfort that you bring this to the researchers attention immediately.

7. What are the possible benefits of taking part?
Whilst there may be no immediate benefits for those people participating in the project it is hoped that this work will lead to improvements in our understanding of the benefits of probiotics.

8. What happens if the research study stops earlier than expected?
You will receive an immediate phone call and reasons will be explained to you. A confirmation letter will be sent to you following the phone call.

9. What if something goes wrong?
If you wish to make a complaint, or have any concerns about the way you have been approached or treated during the course of the study you may contact XXXX

10. Will my taking part in this project be kept confidential?
All the information we receive from you during this study will be anonymised and kept strictly confidential. Only persons running this study will have access to your data.

11. What will happen to the results of the research project?
It is hoped that the results of the study will be published in a scientific journal in the near future, although an exact date cannot be given as yet. If you wish to obtain a summary of the results it is advised that you contact a member of the ProDIBS research team on the contact details below. If you would like a summary of the results these can be sent to you on completion of the research.

12. Who is organising and funding the research?
The research project is organised and by the University of Sheffield and is part-funded by XXXX

13. Who has ethically reviewed the project?
The research project is reviewed and approved by the University of Sheffield Research Ethics Committee. Ref: XXXX

Please note that volunteers who participate in this study will be compensated for their time.

Thank you for taking the time to read this information. If you would like any more information please feel free to contact a member of The ProDIBS Team via telephone on:

XXXX

ProDIBS Team.
Title of Project:
Investigation of the effects of long-term supplementation with probiotics on lower gut microflora and on IBS-D symptoms: The ProDIBS Study

Name of Researcher:

Participant Identification Number for this project:

Please initial box

1. I confirm that I have read and understand the information sheet ................ for the above project and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. .................................................................

3. I understand that my responses will be anonymised before analysis. I give permission for members of the research team to have access to my anonymised responses.

4. I agree to take part in the above research project.

Name of Participant
(or legal representative)

Date
Signature

Name of person taking consent
(if different from lead researcher)

Date
Signature

To be signed and dated in presence of the participant

Copies:

Once this has been signed by all parties the participant should receive a copy of the signed and dated participant consent form, the letter/pre-written script/information sheet and any other written information provided to the participants. A copy for the signed and dated consent form should be placed in the project’s main record (e.g. a site file), which must be kept in a secure location.
Recruitment email: Arm 1

Researchers at The University of Sheffield are currently seeking male volunteers with IBS, preferably working in the vicinity of the XXXX Hospital, for a study looking at the long-term benefits of consumption of probiotics. There is a media and advertising blitz on the use of these health supplements, but as yet little or no data to identify whether the claimed benefits persist on long-term use nor what their mechanism might be. We are looking to recruit 15 male subjects. Subjects will be asked to consume a probiotic, which we will provide, for a six month period. For the six months and for three months before and afterwards, subjects will be asked to provide a stool (poo) sample every 2-3 weeks, and to answer a few short questions about food consumed in the last 24hr and symptoms experienced. The imposition on subjects’ time will be reflected in an honorarium of £300 for completing this study.

*Subjects’ anonymity will be assured*

If you are interested or would like more information, please contact the PROHEMI research team on:

XXXX

Recruitment email: Arm 2

Researchers at The University of Sheffield are currently seeking volunteers with IBS, preferably working in the vicinity of the Royal Hallamshire Hospital, for a study looking at the long-term benefits of consumption of probiotics. There is a media and advertising blitz on the use of these health supplements, but as yet little or no data to identify whether the claimed benefits persist on long-term use nor what their mechanism might be. We are looking to recruit 60 subjects. Subjects will be asked to consume a probiotic, which we will provide, for a six month period. For the six months and for three months before and afterwards, subjects will be asked to answer a few short questions about food consumed in the last 24hr and symptoms experienced. At two points in the study we will request a stool (poo) sample. The imposition on subjects’ time will be reflected in an honorarium of £200 for completing this study.

*Subjects’ anonymity will be assured*

If you are interested or would like more information, please contact the PROHEMI research team on:

prohemi@shef.ac.uk