

# Conducting multinational, cross-cultural research in the functional gastrointestinal disorders: issues and recommendations. A Rome Foundation working team report

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## SUMMARY

### Background

Cross-cultural, multinational research can advance the field of functional gastrointestinal disorders (FGIDs). Cross-cultural comparative research can make a significant contribution in areas such as epidemiology, genetics, psychosocial modulators, symptom reporting and interpretation, extra-intestinal co-morbidity, diagnosis and treatment, determinants of disease severity, health care utilisation, and health-related quality of life, all issues that can be affected by geographical region, culture, ethnicity and race.

### Aims

To identify methodological challenges for cross-cultural, multinational research, and suggest possible solutions.

### Methods

This report, which summarises the full report of a working team established by the Rome Foundation that is available on the Internet, reflects an effort by an international committee of FGID clinicians and researchers. It is based on comprehensive literature reviews and expert opinion.

### Results

Cross-cultural, multinational research is important and feasible, but has barriers to successful implementation. This report contains recommendations for future research relating to study design, subject recruitment, availability of appropriate study instruments, translation and validation of study instruments, documenting confounders, statistical analyses and reporting of results.

### Conclusions

Advances in study design and methodology, as well as cross-cultural research competence, have not matched technological advancements. The development of multinational research networks and cross-cultural research collaboration is still in its early stages. This report is intended to be aspirational rather than prescriptive, so we present recommendations, not guidelines. We aim to raise awareness of these issues and to pose higher standards, but not to discourage investigators from doing what is feasible in any particular setting.

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## INTRODUCTION

Cross-cultural, multinational research can advance the field of functional gastrointestinal disorders (FGIDs) at many levels. While this may appear obvious in terms of prevalence studies, it is less clear, but equally true, that this format can also enhance research in other areas including genetics, psychosocial modulators, symptom interpretation and reporting, extra-intestinal co-morbidity, diagnosis and treatment, determinants of disease severity, health care infrastructure and utilisation, and health-related quality of life; all issues that can be affected by geographical region, culture, ethnicity and race. In addition: (i) evidence of the worldwide prevalence of these disorders lends support to their legitimacy as diagnostic entities, (ii) a similar response to new treatment modalities is compelling evidence of treatment efficacy, (iii) comparisons of FGIDs in populations that differ in ethnicity, diet, exposure to pathogens, history of war trauma, attitudes to illness and culturally defined gender roles may advance our understanding of aetiology, and (iv) comparisons of different health care systems can inform policy decisions.

The increasing interest in research in FGIDs, together with the growing sophistication of communication technology, makes cross-cultural, multinational research feasible. However, advances in study design and methodology, as well as cross-cultural research competence, have not matched technological developments.

The Rome Foundation commissioned a Working Team on Cross-cultural, Multinational Research in the FGIDs to address these issues.<sup>1</sup> The full report of the Rome Foundation, which can be downloaded at [http://theromefoundation.org/committees/multinational\\_com.cfm](http://theromefoundation.org/committees/multinational_com.cfm), reflects an effort by an expert international committee of FGID clinicians and researchers to: (i) define methodological challenges and suggest solutions for study design and research methodology, and (ii) develop recommendations for the fostering of cross-cultural research collaboration.

This paper distils and summarises the working team report, discusses the conduct of cross-cultural FGID research and presents recommendations for its refinement. The objective is to be aspirational rather than prescriptive, so we present recommendations, not guidelines. We aim to raise awareness of these issues and to pose higher standards, but not to discourage investigators from doing what is feasible in any particular setting.

## METHODOLOGICAL ISSUES IN THE CONDUCT OF CROSS-CULTURAL, MULTINATIONAL RESEARCH IN FGIDS

The most common reasons for carrying out multinational or cross-cultural studies are (i) to compare the prevalence of FGIDs in different countries<sup>2</sup> or cultural sub-groups within a country,<sup>3, 4</sup> (ii) to compare health care practices in different countries/cultures,<sup>5-7</sup> and (iii) to test the efficacy of new interventions.<sup>8, 9</sup> These different research aims require different study designs.

The planning stage is critical to the success of any study. Issues that should be addressed in the planning stage of cross-cultural, multinational studies include:

- 1 Study design
  - a. Which protocol and design are best suited to different types of studies:
    - (i) Prevalence studies
    - (ii) Comparison of health care services
    - (iii) Intervention efficacy studies
- 2 Subject recruitment
  - a. Representativeness of samples.
  - b. Categories of study populations.
  - c. Inclusion of children and adolescents.
- 3 Availability of appropriate study instruments
  - a. Translation and validation of study instruments.
  - b. Translatability assessment.
  - c. Translation and validation of study endpoints and outcomes.
  - d. Patient-reported outcomes (PROs) for children and adolescents.
- 4 Documenting confounders
  - a. Characteristics of the cultural sub-groups
  - b. Characteristics of the individual subject
  - c. Implications for study design and analytic plan
- 5 Statistical analyses and reporting of results

### Issues and recommendations

The following is an in-depth discussion of the abovementioned issues. Each section concludes with working team recommendations for future research. As mentioned above, we aim to raise awareness of these issues and to pose higher standards, but not to discourage investigators from doing what is feasible in any particular setting; hence the following are recommendations, not guidelines.

## STUDY DESIGN

### Prevalence studies

Cross-cultural prevalence studies have, by nature, observational designs because study participants cannot be randomised to cultural sub-groups or country of origin. The subjects selected for survey should be as representative of the country of origin as possible and the method of recruiting should be specified. The same methods should be used to recruit and diagnose participants in each country. The respondent in the research is the individual subject, and the interpretability of the data is critically dependent on the use of the same methods to recruit and diagnose patients in each country. Common pitfalls are to use convenience sampling [e.g. employees of a company or agency,<sup>3</sup> students and/or patients from selected medical clinics],<sup>10</sup> rather than random sampling from the population.

Observational cohort studies are never regarded as conclusive because (i) multiple causes interact to produce an outcome such as the development of IBS, (ii) important variables may be unknown or unmeasured, and (iii) there is no practical way of controlling for potential confounders in cross-cultural comparisons; e.g. a study which found large differences in the severity of IBS between countries and attributed those differences to psychosocial variables of interpersonal conflict and family structure, could not rule out other explanations such as ascertainment bias and differences in the understanding of questionnaire items.<sup>10</sup>

#### Recommendations:

- (i) The subjects or clinical practices selected for survey should be as representative of the country of origin as possible, and the method of recruiting should be specified in all subsequent reports and publications.
- (ii) The same methods should be used to recruit and diagnose participants in each country.

### Comparison of health care services

This type of study also requires an observational design, but the respondents may be physicians or public health officials instead of, or in addition to, individual patients.<sup>11</sup> When patients are surveyed, it may be appropriate to recruit them through medical clinics as it is not necessary to include in the survey healthy individuals who do not use health care providers or health care services.

#### Recommendations:

- (i) Studies aimed at comparing health care practices or testing aetiological hypotheses should be limited to no more than four carefully selected cultural groups.<sup>11</sup>
- (ii) These groups should be selected based on a clear contrast among them with respect to the hypothesis, but similarities in other areas.

### Intervention efficacy studies

These studies are usually designed as prospective, randomised controlled trials, and randomisation of patients to treatment arms within each country mitigates concerns about whether the patients are representative of the population, whether they have been recruited in the same way across countries, and whether results can be generalised to all regions. There is evidence that even when standardised in term of definition, there are differences in presentation of FGIDs in different regions. Nevertheless, the use of a consistent recruitment strategy across countries strengthens the generalisability of the findings. A significant but often unrecognised pitfall to multinational drug or other intervention efficacy studies is the use of outcome measures which have not been adequately validated for cultural differences even though they may be linguistically valid. For example, sufferers in some settings for whom respect or authority is strongly valued, may be more reluctant to report pain but more likely to report satisfactory relief of symptoms. In other cases, the study may assess symptoms for which there is no valid translation in some languages, e.g. there is no valid term in Spanish and Italian for the concept of bloating.

## SUBJECT RECRUITMENT

Equivalent methods should be used to enrol patients in all cohorts. However, this may not be feasible if the groups being compared include both developed and developing countries. A standard method of obtaining a population-based sample in developed countries is through a postal survey sent to households randomly selected from electoral roles or random digit dialling of telephone numbers, but developing countries may not have an infrastructure to permit this. House-to-house surveys may be the only possible way of obtaining a population-based sample in this case. In practice, house-to-house surveys have often been done on convenience samples in large cities or near universities, rendering the results unrepresentative of the population.<sup>12</sup>

**Recommendations:**

- (i) Extrapolate valid estimates of disease prevalence, in a population sampled house-to-house in a limited number of locations, by applying statistical methods to adjust for nonrandom sampling. This is a standard epidemiological technique for which the SUDAAN and Stata statistical packages provide built-in algorithms. For a detailed discussion of this technique, see the United Nations publication *ST/ESA/STAT/SER.F/96 'Household Sample Surveys in Developing and Transition Countries'*; see especially Chapter VI: 'Estimating components of design effects for use in sample design'.<sup>13</sup>

**Representativeness of samples**

Many surveys do not use a systematic approach, but instead distribute questionnaires to patients at locations selected for convenience such as the clinics where the investigators work. Often, these are university-based tertiary referral centres that are not representative of the primary care clinics where most health care is delivered; and they may not even be representative of specialty clinics in the country.

While use of a nonsystematic approach limits sample representativeness, studies of nonrepresentative populations may be of interest as long as their composition is clearly defined and not implied to be representative of a larger general population.

**Recommendations:**

- (i) Investigators should avoid using clinic-based sampling to estimate disease prevalence and epidemiology.
- (ii) They should weigh carefully the issue of representativeness before embarking on a survey of health care practices and attempt to survey multiple clinics that are representative of the country.

**Categories of study populations**

There are four basic categories of study populations:

- (i) A genuine community sample, which is required for prevalence studies;
- (ii) A primary care sample, particularly where there is delineation between primary and secondary care with a referral system in place;
- (iii) A secondary care sample, which may include either (i) a mixture of primary and secondary care patients or (ii) patients referred to the secondary

care clinic, even if from within the hospital from a general clinic;

- (iv) Patients seen in tertiary care.

Prevalence studies are the only types that require population-based sampling. In other types of cross-cultural research, where the goal is to compare health care practices between cultural groups or to test hypotheses about aetiological mechanisms, samples recruited through clinics may be appropriate.

Differing health systems will provide differing populations for surveys. In countries with a formal primary-secondary divide, a wider population will be reached in primary care, and patients referred to secondary care will comprise a selected population. In contrast, where patients are able to access hospital services or specialists directly, (even if on the basis of a primary care approach) there will be a mix of populations. Tertiary care centres will have a highly selected population, which likely includes patients with more severe symptoms.

**Recommendations:**

- (i) Reports of studies should clearly define the population and method of recruitment so that comparisons between settings are more meaningful.
- (ii) Protocols or templates should be used that provide specific study method details. Completed templates could be attached to studies and papers based on them, to enable the interpretation of data more usefully.
- (iii) Journal editors should require the authors of surveys to address, in detail, the representativeness of the subjects.

Different health systems, variations in clinician behaviour in interpreting and diagnosing functional problems, and differences in specific data collection methodologies all contribute to challenges in enrolling comparable cohorts in a cross-cultural study. Emphasis should be placed on like-to-like comparisons to avoid erroneous conclusions. A more universally applicable approach should be aspired to, as different cultural and system concepts may impede realisation of this goal. An alternative is to report data on functional problems from different settings with a clear acknowledgement of differences in methodology and populations between study sites.

**Inclusion of children and adolescents**

There is extremely limited published literature in which children and adolescents in different countries

with distinct cultural backgrounds have been included as participants in surveys or even the inclusion of families from different ethnic backgrounds in surveys.

The same methodological issues that may confound cross-cultural comparisons in adults (e.g. differences between countries in diet, genetic make-up, and exposure to pathogens) also exist for children. In addition, investigators should carefully consider whether there are other cultural differences, which may affect the outcomes of child health surveys:

- (i) In some cultures, there are strong preferences for having male children. These cultural preferences may also be reflected in whether male children are more likely than female children to be taken to a physician when ill and in how they are treated.
- (ii) Other variables to consider are:
  - The average number of children per family.
  - The family member typically responsible for child rearing, e.g. grandmother, mother, older child, day-care worker.
  - Child labour practices, and involvement of children in begging, the sex trade or by guerrilla armies, all of which may contribute to physical or mental trauma.

#### AVAILABILITY OF APPROPRIATE STUDY INSTRUMENTS

A large proportion of cross-cultural studies are based on questionnaires. The most frequently employed are (i) diagnostic questionnaires that incorporate symptom-based diagnostic criteria;<sup>14</sup> (ii) disease-specific severity measures;<sup>15–17</sup> and (iii) generic or disease-specific health-related quality of life scales.<sup>18, 19</sup> Other types of questionnaires that are appropriate for inclusion in cross-cultural surveys are psychological symptom scales,<sup>20</sup> somatisation scales<sup>21</sup> and cognitive scales.<sup>22</sup>

Most of the questionnaires identified as appropriate for inclusion in cross-cultural studies were developed and written in English and designed for western populations, so the methodology is potentially ethnocentric and, at times, inappropriate. Some of them have been translated into other languages, with or without a process of cultural adaptation. To our knowledge, no database has been prepared with information on study instruments related to FGID research that are available in different languages.

#### Recommendations:

- (i) The Rome Foundation should appoint a committee to survey the literature, the Internet and other

potential sources of translated study instruments, and canvas investigators in the field.

- (ii) This committee should prepare a database of available instruments with information such as type, potential use in studies, relevant citations, available languages, method of validation, instrument assessment, and copyright restrictions.
- (iii) This 'library' of study instruments, preferably in pdf form, would be maintained by the Rome Foundation and accessible to researchers conducting cross-cultural studies.

#### Translation and validation of study instruments

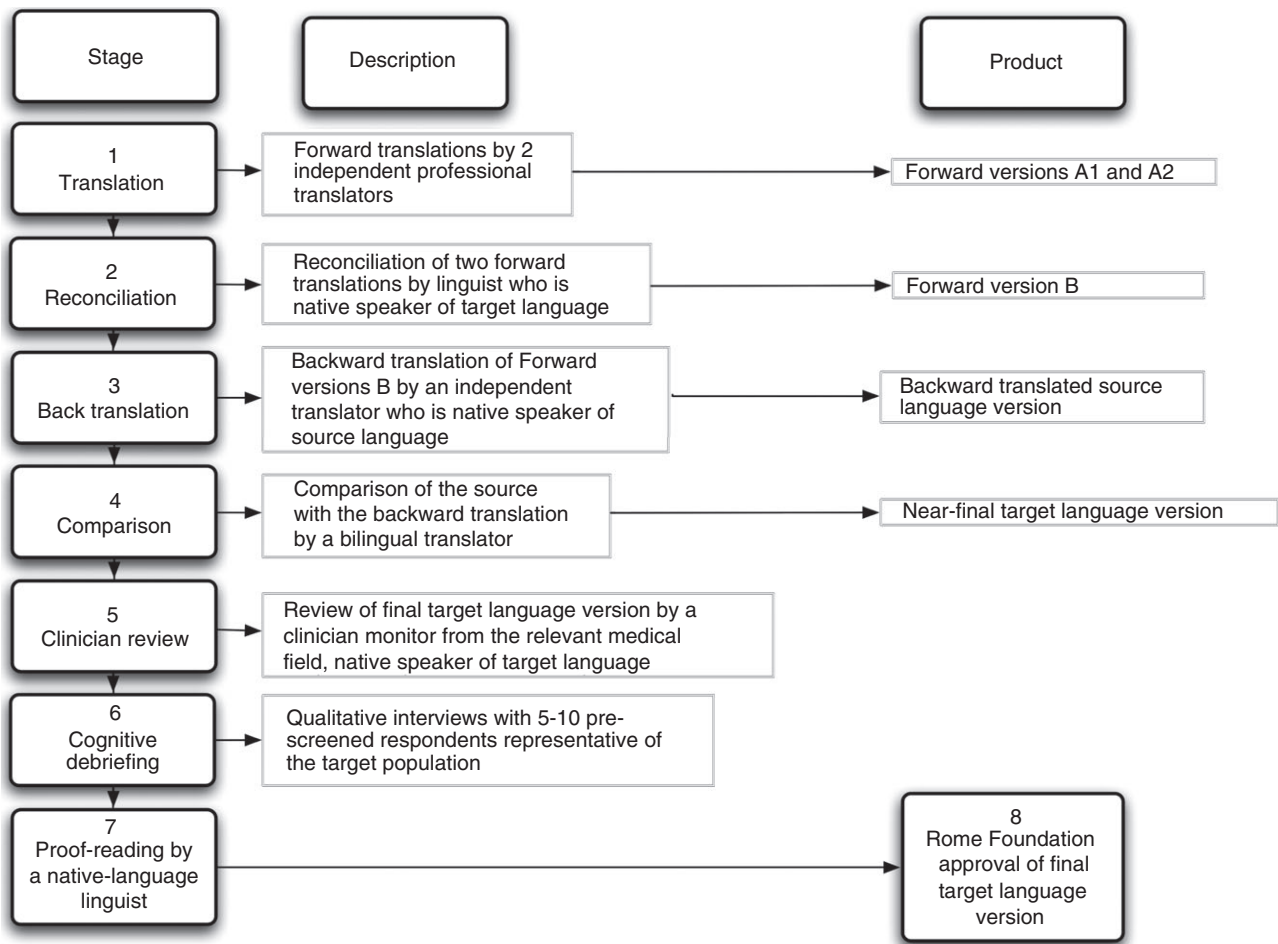
The need for the translation of study material into different languages is steadily increasing and has become a cornerstone of modern research.<sup>23</sup> However, cross-cultural translation has pitfalls that threaten validity. Some of these pitfalls are difficult to detect unless a rigorous and standardised methodological process is adopted. Failing to do this could have unrecognised, deleterious effect on study results.<sup>24</sup>

Cross-cultural translation is a process that involves both formal language and cultural adaptation in the process of preparing an instrument for use in another culture. The challenge is to adapt an instrument so that it retains the meaning and intent of the original instrument (the source language), yet is culturally relevant and comprehensible for the target population,<sup>25</sup> i.e. a 'conceptually equivalent' rather than a 'literal' translation. To this end, advanced planning is essential<sup>26–28</sup> to maximise the effectiveness of the dual processes of translation and adaptation. The process of translating and adapting a questionnaire for a different cultural group can be arduous and requires a considerable investment of time and money. However, unless this process is adopted and successfully implemented, the validity of the research results would be suspect.

The translation process adopted and recommended by most associations and commercial translation companies today are similar to each other in structure and content and usually include some variation of the steps described below. The Rome Foundation has adopted a similar approach in the guidelines for translation of its documents as can be seen on its website at <http://www.rome-criteria.org/translations> (full details, including a flow diagram can be found in Figure 1).

#### Translatability assessment

Translatability assessment is a recently developed process aimed at identifying potential translation and adaptation



**Figure 1 |** Rome Foundation translation and cultural adaptation process.

problems in the initial instrument development stage in the source language.<sup>29</sup> Conducting a translatability assessment during the instrument development stage can avert challenges in concept adaptation and equivalency when instruments are later translated for use in global studies. If potentially problematic items are identified in development, they can be revised, removed, or replaced to create a source language instrument better positioned for translation with fewer conceptual equivalence difficulties.

#### Translation and validation of study endpoints and outcomes

The translation of endpoints for clinical trials bears a more significant weight than translation of other more general documents, such as questionnaires, due to the critical role of primary and secondary endpoints. If the language in any way impedes the appropriate comprehension of the questionnaire by the patient, the implications for the data

and therefore the economic consequences can be enormous. Translation professionals should consider the responsiveness of the endpoints as well as equivalence in meaning across settings, i.e. whether taboos or social mores may limit the patient's use of a response scale more in one culture than in another.<sup>30</sup>

#### Recommendations:

- (i) Without appropriate translation and cultural adaptation of research instruments into target languages quality multinational, cross-cultural studies are not feasible.
- (ii) All future multinational studies on the FGIDs need to be cognizant of and adopt guidelines for the translation and cultural adaptation of the instruments used, including familiarity with the process of translatability assessment and issues specifically related to the translation of endpoints and outcomes.

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- (iii) The Rome Foundation translation guidelines should be followed in translating and validating FGID study instruments in other languages.
- (iv) Translation professionals should consider the responsiveness of endpoints as well as the equivalence in meaning across settings.

### PROs for children and adolescents

In its guidance for industry on PROs published in 2009<sup>31</sup>, the FDA stated that in addition to issues that are common to children and adults, specific issues for PRO instruments applied in children and adolescents include:

- (i) Age-related vocabulary.
- (ii) Language comprehension.
- (iii) Comprehension of the health concept measured.
- (iv) Duration of recall.

They further recommend that instruments should be developed for fairly narrow age groupings to account for developmental differences and to determine the lower age limit at which children can understand the questions and provide reliable and valid responses that can be compared across age categories.

#### Recommendations:

- (i) The process for obtaining consent from parent and/or child in each country should be described in the report of the study.
- (ii) The Rome Foundation should prepare guidelines for the development and cross-cultural translation and validation of health-related questionnaires, PROs and other instruments for children.

## DOCUMENTING CONFOUNDERS IN CROSS-CULTURAL RESEARCH

### Characteristics of cultural sub-groups

The observed differences between cultural groups could be attributable to one or more of the following variables that differ between countries and cultures:

- (i) Differences in the typical diet (e.g. fibre content, infant or adult nutrition).
- (ii) Pathogen exposure, e.g. likelihood of exposure to enteric pathogens and type of pathogens.
- (iii) Health care delivery models, e.g. Western vs. traditional healers, national health insurance vs. private pay.
- (iv) Open access vs. strict referral system.

- (v) Illness explanatory models, e.g. micro-organisms, psychosocial factors, religious and spiritual factors.
- (vi) Difference in cultural taboos in discussing topics such as defecation, sexual abuse and mental illness.
- (vii) Gender, racial and adult vs. child differences in access to and utilisation of health care.
- (viii) Education and literacy rates.
- (ix) Language diversity (e.g. how many languages are commonly spoken).
- (x) Major religions and religious diversity.

When investigators recognise that these factors could account for differences between cultural groups, they usually measure them and use statistical tests to determine whether they could be mediators of the study's primary outcomes. In some studies, however, such factors are not measured, hence becoming potential *confounders*, which could undermine the study's conclusions.

### Characteristics of the individual subject

There is also diversity between individuals within a sample, so it is useful to identify important characteristics of each subject. Gender, race and age are usually recorded. Beyond this, we suggest that the following characteristics be collected in multicultural settings:

- (i) Primary language and whether different from language of interview.
- (ii) Education level or at least the ability to read.
- (iii) Whether the subject lived and/or was educated abroad.
- (iv) Usual health care provider (Western-trained or traditional).
- (v) Socioeconomic status.
- (vi) Social support.
- (vii) Urban vs. rural residence.
- (viii) Exposure to war or political turmoil.

## IMPLICATIONS OF POTENTIAL CONFOUNDERS FOR STUDY DESIGN AND ANALYTIC PLAN

Studies should be designed so that the statistical analysis can distinguish between the impact of these potential confounders vs. the impact of other differences between cultures that are of primary interest to the investigator. For example, in comparing the prevalence of bloating in Asian and European countries if the investigators recognise that there are differences in both diet and pathogen exposure between most Asian vs.

most European countries in their sample, they may need to ensure that there is enough diversity in the diets and pathogen exposure of individuals in the two cohorts to be able to treat diet and pathogen exposure as covariates in the analysis. In some cases, it may be necessary to admit that it is not possible to statistically adjust for such confounders and that any differences in outcome could reflect the effects of these confounder or mediator variables.

## STATISTICAL ANALYSES AND REPORTING OF RESULTS

The demographical tables describing the subjects included in the study should be expanded to include other characteristics likely to differ between cultures and to influence the results of the cross-cultural comparison. These may include:

- (i) Literacy, native language and whether it is the primary language of the country.
- (ii) Religious affiliation.
- (iii) Proportion of subjects who were educated abroad.
- (iv) Use of 'traditional' vs. western providers for health care.

Other potential confounders that should be considered are listed in the section on 'Documenting confounders in cross-cultural research' (above).

## SUMMARY

Because of technological advances in global communication and growing recognition of the potential contribution of multinational, cross-cultural research, it is increasingly important to define problems in this type of research and propose solutions for them. Knowledge of

the problems and potential solutions will increase research competence resulting in a greater degree of confidence in the accuracy of research results.

While this paper focused on potential benefits for cross-cultural, multinational research specifically for FGIDs, it is our belief that similar benefits can be expected in all other areas of GI research, because cross-cultural comparisons can highlight issues related to all research areas alluded to in the introduction, not necessarily confined to the field of FGIDs.

As stated above, the objective of this paper is to be aspirational rather than prescriptive, so we present recommendations, not guidelines. We aim to raise awareness of these issues and to pose higher standards, but not to discourage investigators from doing what is feasible in any particular setting.

## AUTHORSHIP

*Guarantor of the article:* Ami D. Sperber.

*Author contributions:* Each of the authors participated in working team meetings and conference calls, contributed to the conceptualisation and implementation of the working team process and took responsibility for specific sections of the report, including literature searches and writing of the section. All authors reviewed and approved the final manuscript.

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