

**Final Report**  
**Rome Foundation Working Team**

**on**

**Conducting Multinational, Cross-cultural Research in the Functional GI  
 Disorders and Fostering Multinational Research Networks**

***Chair:***

**Ami D. Sperber MD, MSPH, Israel**

***Sub-committee chairs:***

**Kok Ann Gwee MD, PhD, Singapore; A Pali Hungin MD, UK; William Whitehead PhD, USA**

***Working team members:***

**Enrico Corazziari, MD, Italy; Shin Fukudo, MD, PhD, Japan; Charles Gerson MD, USA;**

**Uday C. Ghoshal, MD, DM, India; Jin-Yong Kang, MD, PhD, UK/Singapore;**

**Rona L. Levy, MSW, PhD, MPH, USA; Max Schmulson MD; Mexico**

***Working team consultants:***

**Dan Dumitrascu MD, Romania; Mary-Joan Gerson PhD, USA; Chen Minhu MD, PhD, China;**

**Seung-Jae Myung MD, PhD, South Korea; Eamonn Quigley MD, Ireland/USA;**

**Peter Whorwell, MD, UK; Katie Zarzar, USA**

**January 2014**



## Table of Contents

<b>Introduction .....</b>	<b>3</b>
<b>Section 1. Methodological Issues in the Conduct of Cross-cultural, Multi-national Research in FGIDs .....</b>	<b>4</b>
<b>1.1 Study design.....</b>	<b>5</b>
1.1.1 Prevalence studies .....	5
1.1.2 Comparison of health-care practices .....	5
1.1.3 Drug efficacy studies .....	5
1.1.4 Potential confounders.....	6
1.1.5 Subject recruitment .....	6
1.1.6 Representativeness of samples .....	6
1.1.7 Categories of study populations .....	6
1.1.8 Other potential factors to consider .....	7
<b>1.2 Availability of appropriate study instruments .....</b>	<b>8</b>
<b>1.3 Translation and validation of study .....</b>	<b>8</b>
<b>1.4 Guidelines for documenting confounders in cross-cultural research .....</b>	<b>10</b>
1.4.4 Inclusion of children and adolescents .....	11
<b>1.5 Statistical analyses and reporting of results .....</b>	<b>12</b>
<b>Table 1. Diagnostic questionnaires, severity scales, and quality of life scales .....</b>	<b>13</b>
<b>Table 2: Psychological scales for use in cross-cultural studies .....</b>	<b>15</b>
<b>Table 3. Points of contention relating to cross-cultural differences in symptom reporting of bloating, distension, and fullness. ....</b>	<b>16</b>
<b>Section 2. Fostering Research Networks and Multinational Research Collaboration in FGIDs.18</b>	
<b>2.1 Guidance for developing multi-national research networks.....</b>	<b>19</b>
2.1.1 Conditions for fostering research networks .....	19
2.1.2 Organization of networks: infrastructure, administration, and communication .....	19
2.1.2.1 Conference calls (including video-conferencing).....	19
2.1.2.2 Email .....	19
2.1.2.3 Internet .....	20
2.1.3 Identifying funding sources and collaborators .....	20
2.1.4 Logistic barriers .....	20
2.1.5 Potential research areas for cross-cultural research in the FGIDs.....	20
2.1.5.1 Project - The challenge of language in the subjective reporting of fullness, bloating and distension .....	21
2.1.5.2 Project - Comparison of the health care infrastructure in South Korea, India, Italy, and Mexico .....	22
<b>Appendix 1. Translation and validation of study instruments .....</b>	<b>23</b>
<b>Appendix 2. Existing Multi-national FGID Research Networks.....</b>	<b>27</b>
<b>Appendix 3. Identifying funding sources and potential collaborators for multinational research in FGIDs.....</b>	<b>29</b>
<b>Appendix 4. Challenge of culture and language in symptom reporting: bloating, distension, and fullness. ....</b>	<b>31</b>
<b>Appendix 5. A Comparison of healthcare services among four countries and their implications for diagnosis and care of FGID patients .....</b>	<b>33</b>
<b>Appendix 6. Cross-cultural multinational research: intra-family illness behavior dynamics.....</b>	<b>39</b>
<b>Fig. 1. Rome Foundation translation and cultural adaptation process.....</b>	<b>43</b>
<b>Bibliography .....</b>	<b>44</b>

## Introduction

Cross-cultural, multi-national research has the potential to advance the field of functional gastrointestinal disorders (FGIDs) at many levels. In addition to FGID prevalence studies, cross-cultural comparative research can make a significant contribution in genetics, psychosocial modulators, symptom reporting, symptom interpretation and symptom presentation, extra-intestinal co-morbidity, diagnosis and treatment, determinants of disease severity, healthcare infrastructures, health care utilization, and health-related quality of life; all issues that can be affected by culture, ethnicity, and race.

In addition, (a) evidence of the world-wide prevalence of these disorders can lend support to their legitimacy as diagnostic entities, (b) when patients in different countries show a similar response to treatment with a new drug or other therapy there is compelling evidence of treatment efficacy, (c) comparisons of the prevalence and characteristics of these disorders in populations which differ in important dimensions such as diet, exposure to pathogens, history of war trauma, and culturally defined gender roles may advance our understanding of their etiology, and (d) comparisons of different health care delivery systems can inform policy decisions about cost-effective ways to manage these disorders and may identify potential pitfalls. (1-3)

The increasing interest in research in IBS and other functional gastrointestinal disorders (FGIDs), taken together with the growing sophistication of communication technology, makes cross-cultural, multi-national research a feasible endeavor. For example, the development of global Internet access and low-cost telephone and video-conferencing technologies has created an unprecedented opportunity for real-time communication for the efficient conduct of cross-cultural research.

However, advances in study design and methodology as well as cross-cultural research competence have not matched these technological developments and this has impeded the achievement of significant progress. Furthermore, the development of multinational research networks and cross-cultural research collaboration is still in its early stages.

This report reflects an effort by an international committee of FGID clinicians and researchers to: (a) better define these methodological challenges and suggest possible solutions, and (b) to develop

recommendations for the fostering of cross-cultural research collaboration and networks.

To accomplish these objectives the working team formed sub-committees that addressed the various specific issues involved, reported on them and made specific recommendations relating to them.

This report contains a central document, in two parts, and appendices with the individual sub-committee reports.

The first part of the report addresses issues in study design and research methodology and proposes recommendations to improve these aspects of FGID research.

The second part discusses issues related to the fostering of multi-national research networks and presents potential research areas with examples of specific study proposals involving cross-cultural issues that could benefit from multi-national collaboration.

The appendices provide an in-depth review of the various issues addressed, for readers who are interested in further details.

## **Section 1. Methodological Issues in the Conduct of Cross-cultural, Multi-national Research in FGIDs**

### ***Sub-committee chairs:***

**A Pali Hungin MD, UK; William Whitehead PhD, USA**

### ***Sub-committee members:***

**Enrico Corazziari, MD, Italy; Uday C. Ghoshal, MD, DM, India;**

**Jin-Yong Kang, MD, PhD, UK/Singapore; Rona L. Levy, MSW, PhD, MPH, USA;**

**Ami D. Sperber MD, MSPH, Israel**

### ***Sub-committee consultant:***

**Katie Zarzar, USA**

## 1.1 Study design

The most common reasons for carrying out multinational or cross-cultural studies are (a) to compare the prevalence of FGIDs in different countries (4) or cultural subgroups within a country (5, 6), (b) to compare health-care practices in different countries/cultures (7-9), and (c) to test the efficacy of new drugs (10, 11). These different research aims require different study designs.

### 1.1.1 Prevalence studies

Prevalence studies require an observational study design because the subjects cannot be randomly assigned to cultural subgroups; this distinguishes cross-cultural studies from experimental studies and has important implications for the generalizability of findings.

Because the research design is observational, the groups have to be recruited by the same methods to insure that observed differences between cultural subgroups are not an artefact of the recruitment method. The denominators have to be as similar as possible when inferring prevalence differences.

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 (5) or patients from selected medical clinics (12), rather than random sampling from the population. The translation and cross-cultural validation of study questionnaires embodying diagnostic criteria is also important to prevalence studies. Observational cohort studies are never regarded as conclusive because (a) multiple causes interact to produce an outcome such as the development of IBS, (b) important variables may be unknown or unmeasured, and (c) there is no practical way of controlling for potential confounders in cross-cultural comparisons; for example, a study (12) 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.

Experimental study designs in which subjects are randomly assigned to groups yield results that are more conclusive because random assignment balances the groups on

variables unrelated to the hypothesis; however, such experimental designs are not possible in cross-cultural research.

### Recommendation #1

- *Cross-cultural studies are, by nature, observational study designs because study participants cannot be randomized to cultural sub-groups or country of origin.*
- *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.*
- *The same methods should be used to recruit and diagnose participants in each country.*

### 1.1.2 Comparison of health-care practices

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

### Recommendation #2

- *Studies aimed at comparing health care practices or testing etiologic hypotheses should be limited to only a few carefully selected cultural groups.*
- *These groups should be selected based on a clear contrast with respect to the hypothesis, but similarities in other areas.*

### 1.1.3 Drug efficacy studies

These studies are usually designed as prospective, randomized controlled trials, and randomization of patients to treatment arms within each country mitigates concerns about whether the patients are representative of the population and whether they have been recruited in the same way across countries.

There is also evidence that even when standardized in term of definition, there are differences in presentation of FGIDs in different regions.

### Recommendation #3

- *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 clustered sampling, including the application of weights to responses to adjust the demographics of the sample to the demographics of the population.*

Nevertheless, the use of a consistent recruitment strategy across countries strengthens the generalizability of the findings.

Because IBS is a female-predominant disorder in most countries there is a potential problem in achieving statistical power for the male sub-group, for example in some Western drug trials there were only a few male patients with IBS enrolled. Therefore, these studies did not have sufficient statistical power to determine efficacy among male patients.

A significant but often unrecognized pitfall to multinational drug 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 individuals from some Asian countries for whom respect for authority is strongly valued, may be more reluctant than Western subjects to report pain but more likely to report satisfactory relief of their symptoms.

#### 1.1.4 Potential confounders

There are many potential confounders that could undermine the interpretation of cross-cultural comparisons – so many that it is not possible to identify and measure them all or to adjust for them (see section on guidelines for documenting confounders, section 1.4 below). The greater the number of different countries or cultural groups included in the study, the greater is the risk that unmeasured confounders could account for findings (or for a failure to confirm a hypothesis).

#### 1.1.5 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. The 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 do not have the infrastructure that permits this. House-to-house surveys may be the only possible way of obtaining a population-based sample in developing countries. In practice, house-to-house surveys have often been done on convenience samples in large cities or near

### Recommendation #4

- *Investigators should avoid using clinic-based sampling to estimate disease prevalence and epidemiology.*
- *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.*

universities, rendering the results unrepresentative of the population. These techniques are frequently used by the U.S. National Center for Health Statistics in surveys such as the National Health and Nutrition Examination Survey of the U.S. population ([www.cdc.gov/nhanes](http://www.cdc.gov/nhanes)).

#### 1.1.6 Representativeness of samples

Publications on disease prevalence and epidemiology often rely on surveys of clinic patients. In countries such as Sweden and Great Britain where the National Health Service requires that all individuals be identified with one and only one primary care physician, this may result in a representative sample. However, many surveys do not use this systematic approach, but instead distribute questionnaires to the patients at clinics selected for convenience such as the clinics where the investigators work. Often they are university-based tertiary referral centers 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 non-systematic approach limits sample representativeness, studies of non-representative populations may be of interest as long as their composition is clearly defined and not implied to be representative of a larger general population.

#### 1.1.7 Categories of study populations

There are four categories of populations for study:

A genuine **community sample**, which is required for prevalence studies;

A **primary care sample**, particularly where there is delineation between primary and secondary care with a referral system in place;

A **secondary care sample**, which may include either (a) a mixture of primary and secondary care patients or (b) patients referred to the secondary care clinic, even if from within the hospital from a general clinic;

Patients seen in tertiary care. Note that definitions of tertiary care can vary geographically. For example, in open health care systems in some countries such as India, some "tertiary care" hospitals also work as primary and secondary care centers. When a patients present to a hospital by self-referral the hospital cannot refuse to see them.

#### **Recommendation #5**

- *We recommend the use of a template that provides specific study method details. This completed template could be attached to studies to enable the interpretation of data more usefully.*
- *We also recommend that journal editors require the authors of surveys to address the representativeness of the subjects.*

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 etiologic 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 centers will have a highly selected population, which likely includes more severe patients.

#### **Action point #1**

- *The Rome Foundation should use a template similar to the one recommended by the CONSORT guidelines, which provides a standardized way of reporting differences in cross-cultural studies, is recommended.*

It is important that reports on the study should clearly define the population and method of recruitment so that comparisons between settings are more meaningful.

#### **1.1.8 Other potential factors to consider**

The recruitment of subjects also depends on cultural norms in terms of participating in research and whether incentives are provided to clinicians or patients.

Variations between physicians in different countries and in different medical subspecialties within a country in terms of their attitudes towards FGIDs and their approach to diagnosis of these disorders may also have an impact on surveys of disease prevalence and epidemiology. For example, a hospital-based population may be more suitable for categorization into IBS using the ROME criteria, but primary care populations may be diagnosed on a different basis. Cultural and regional differences in the attitudes of patients towards functional disorders may also impact health surveys; for example the reluctance of women in some cultures to report bowel-related symptoms as well as the lack of access for females to health care. In regions where human immune-deficiency (HIV) is endemic, patients may be less likely to identify themselves as having an FGID such as IBS, and their physicians may also be reluctant to diagnose IBS because the symptoms of IBS are suggestive of HIV. These variations between countries need to be better understood.

#### **Study design - Summary**

- *Different health systems, variations in clinician behavior 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.*
- *We should work towards a more universally applicable approach (as much as possible with different cultural and system concepts).*
- *An alternative is to report data on functional problems from different settings with a clear acknowledgment of differences in methodology and populations between study sites.*

## 1.2 Availability of appropriate study instruments

A large proportion of cross-cultural studies are based on questionnaires. The most frequently employed are (a) diagnostic questionnaires which incorporate symptom-based diagnostic criteria; (b) disease-specific severity measures; and (c) generic or disease specific health-related quality of life scales (see Table 1 for examples). Other types of questionnaires that are appropriate for inclusion in cross-cultural surveys are psychological symptom scales, somatization scales, and cognitive scales (see Table 2 for examples).

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. Often these translations were prepared for specific projects (13, 14). To our knowledge no database has been prepared with information on study instruments related to FGID research that are available in different languages. Tables 1 and 2 identify the questionnaires known to the authors, which are available in languages other than English. However, this list is incomplete.

At present the only questionnaire listed in Table 1 that has been translated and validated in multiple languages is the Rome III Diagnostic Questionnaire (15). This questionnaire was developed by the Rome Foundation to be used by clinicians as an aide to diagnosis of the FGIDs and also to be used by researchers for epidemiologic surveys and inclusion criteria in clinical trials. In response to frequent requests for the questionnaire in different languages, the Rome Foundation established guidelines for translation and validation and has a process for approval of translations. The translations which have been approved by the foundation are posted on its website ([www.romecriteria.org](http://www.romecriteria.org)) and made available to researchers and clinicians.

Currently the Rome criteria are being updated, and a new Rome Diagnostic Questionnaire will be created to embody the revised criteria. To facilitate the translation of the Rome IV Diagnostic Questionnaire into other languages, the draft questionnaire will undergo a translatability assessment (see 1.3.2, below) to insure that there are no ethnocentric

barriers to its translation into the major languages of the world.

### Recommendation #6

- *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.*
- *The final product would be 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.*
- *This "library" of study instruments, preferably in pdf form, would be maintained by the Rome Foundation and accessible to researchers conducting cross-cultural studies.*

## 1.3 Translation and validation of study

(see Appendix 1 for the full version of this section)

The need for the translation of study material into different languages is steadily increasing and has become a cornerstone of modern research (16). However, cross-cultural translation has pitfalls that threaten validity. Some of these pitfalls are difficult to detect unless a rigorous and standardized methodological process is adopted. Failing to do this could have unrecognized, deleterious effect on study results (17). Thus, flawed methodology may lead to erroneous research conclusions, which, although due to technical flaws, are undetectable as such and considered to be substantive in nature.

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) and is culturally relevant and comprehensible for the target culture (18). Thus, the aim is to achieve a "conceptually equivalent" rather than a "literal" translation. To this end advanced planning is essential (19-21) so that the dual processes of translation and adaptation will be as effective as possible. 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.

### **1.3.1 Guidelines for translation and adaptation of questionnaires**

Because of the growing importance of translation for international studies, several developments have taken place over recent decades. These include:

- An increasing understanding of the need to anticipate potential difficulties in translation when developing a new questionnaire (21). This process, known as “translatability assessment,” is discussed below (1.3.2).
- The efforts of the FDA and other regulatory agencies to make the development and translation of PROs a uniform, consistent process (22).
- The work of multinational professional societies and associations dedicated to the refinement of research methods, particularly in the area of outcomes research. These organizations have published guidelines relating to cross-cultural translation, translatability assessment, and migration from PROs to e-PROs, as discussed below. Examples of this are the European Organization for Research and Treatment of Cancer (EORTC), which has developed quality of life instruments and carefully monitored their translation into multiple languages, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Both of these organizations have published relevant translation and migration guidelines (23-25).
- The increasing presence and importance of commercial companies that specialize in the translation of research instruments for multinational studies.

The translation process adopted and recommended by most associations and commercial translation companies today are similar 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.romecriteria.org/translations>. (Full details, including a flow diagram can be found in Appendix 1.)

### **1.3.2 Translatability assessment**

Translatability assessment is a recently developed process aimed at identifying potential translation and adaptation problems in the initial instrument development stage in the source language. Instruments are often developed for immediate use in the local target population without consideration for future global application. Conducting a translatability assessment during the instrument development stage prevents 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. While not every cultural and linguistic challenge can be eliminated via translatability assessment, many can be prevented via the selection of alternative options or the removal of items that are too culturally specific to be effectively adapted.

#### **Recommendation #7**

- *Future iterations of Rome criteria and study questionnaires constructed in English should as far as possible employ culturally neutral terms with unambiguous descriptors.*
- *Translatability assessment should be used when new questionnaires are being developed in one source language.*

### **1.3.3 Translation and validation of endpoints**

The translation of trial endpoints can be problematic due to the language present in the source (English) questionnaire to be translated. Due to the critical nature of the data gathered by endpoints supporting labelling claims, it is critical that these risks are mitigated via a translatability assessment.

The translation of endpoints bears a more significant weight than translation of other more general documents in a trial due to the critical role of primary and secondary endpoints in a trial. 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. As with literal translation, translation and cultural adaptation (linguistic validation) of instruments face challenges resulting from linguistic and

cultural differences across target countries. These challenges and differences in language, if not appropriately managed, can directly impact the validity of the data gathered in a global clinical trial.

The importance of defining each item's conceptual meaning is the most critical step in mitigating this risk. By defining in detail each item's intended meaning, listing approved synonyms, and listing terms or descriptors that would detract from the item's intended meaning, we can provide the linguists with the specific guidance necessary to develop conceptually equivalent content in the target language version. Immediately following concept definitions, the selection of appropriate translation partners, linguists, clinician consultants, and cognitive interviewers to conduct the qualitative patient interviews with respondents in each target country is vital to mitigating the problems involved in translation and cultural adaptation of endpoints. These experts 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.

#### **1.3.4 Migration of PROs to e-PROs – measurement equivalence**

Patient-reported outcome (PRO) data are collected directly from patients. PROs are often used to measure treatment efficacy in clinical trials, and may serve as primary or secondary end-points. To date, PRO data have typically been collected using paper-and-pencil measures. However, electronically administered PRO measures (ePROs) are increasingly being used (26).

An ePRO has been recently developed that allows physicians to assess the clinical course of their IBS patients. This technique could easily be adapted to compare the constancy or variation of IBS symptoms over time in IBS populations in different geographic areas (27). Understandably, there was uncertainty regarding the “migration” of PROs to the electronic environment and studies have been conducted to evaluate the process and formulate guidelines for future practice (24, 28). This is particularly important in light of the interest expressed in this issue by the FDA and other regulatory agencies (22).

One meta-analysis synthesized 65 studies that directly assessed the equivalence of computer versus paper versions of PROs used in clinical trials. A total of 46 unique studies,

evaluating 278 scales, provided sufficient detail to allow quantitative analysis. The investigators found that extensive evidence indicates that paper- and computer-administered PROs are equivalent and that validation studies should not generally be required when migrating a PRO measure from paper to computer, although cognitive interviewing may be useful to ensure that patients are interpreting the migrated or reformatted items in the intended manner (28).

#### **Translation and Validation - Summary**

- *It is becoming increasingly clear that without appropriate translation and cultural adaptation of research instruments into target languages quality multinational, cross-cultural studies are not feasible.*
- *All future studies on 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 related to the migration of PROs to ePROs.*

#### **Action point #2**

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

### **1.4 Guidelines for documenting confounders in cross-cultural research**

#### **1.4.1 Characteristics of the cultural subgroups**

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

- Differences in the typical diet (e.g., fiber content, infant or adult nutrition).
- Pathogen exposure (e.g., likelihood of exposure to enteric pathogens and type of pathogens).

- Health care delivery models (e.g., Western vs. traditional healers, national health insurance vs. private pay).
- Open access versus strict referral system.
- Illness explanatory models (e.g., micro-organisms, psychosocial factors, religious and spiritual factors).
- Difference in cultural taboos in discussing topics such as defecation, sexual abuse, and mental illness.
- Gender, racial, and adult vs. child differences in access to and utilization of health care.
- Education and literacy rates.
- Language diversity (e.g., how many languages are commonly spoken).
- Major religions and religious diversity.

When investigators recognize 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, these factors are not measured, and they are potential confounders, which could undermine the study's conclusions.

#### **1.4.2 Characteristics of the individual subject**

There is also diversity between the 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:

- Primary language and whether different from language of interview.
- Education or at least the ability to read.
- Whether the subject lived and/or was educated abroad (communication from working team members).
- Usual health care provider (Western-trained or traditional).
- Socioeconomic status.
- Social support
- Urban vs. rural residence.
- Exposure to war.

#### **1.4.3 Implications for study design and analytic plan**

The study 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, if the investigators are comparing the prevalence of bloating in Asian

and European countries and they recognize that there are differences in both diet and pathogen exposure between most Asian vs. most European countries in their sample, they may need to insure 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 the conclusions of the study will have to acknowledge that differences in outcome could reflect the effects of these confounder or mediator variables.

#### **1.4.4 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 within the United States. Thus, our suggestions are based on opinion and limited experience.

In the US, children below the age of 7 are often regarded as unreliable responders, and surveys about their health status are addressed to their parents, and typically, due to availability, to their mothers. We expect that in other countries, interviewing parents about the health status of young children will also be appropriate. The process for obtaining consent from parent and/or child in each country should be described in the report of the study. For example, in the United States a study cannot be published without confirmation that parents gave consent and, separately, children assented to participation in the study.

Older children and adolescents may be asked to respond for themselves. However, developmental differences are known to be an important source of variability in health surveys completed by children and adolescents, and many instruments such as the Child Behavior Checklist (29) have gender and age adjusted norms for scoring and interpretation.

The majority of pediatric symptom questionnaires and health survey instruments were developed in English, and a few have been translated into other languages. We are

unaware of any published guidelines for the translation and cross-cultural validation of health questionnaires for children.

### **Action point #3**

- *The Rome Foundation should prepare guidelines for the cross-cultural translation and validation of health questionnaires and other instruments for children.*

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), exist also for children. In addition, investigators should carefully consider whether there are other cultural differences, which may affect the outcomes of child health surveys. For example, 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. Other differences that affect the social environment in which children grow up include the average number of children per family, the family member who is typically responsible for child-rearing (e.g., grandmother, mother, older child, day-care worker), child labor practices, and involvement of children in begging, the sex trade or by guerrilla armies, all of which may contribute to physical or mental trauma.

Other differences which could affect pediatric investigations include cultural differences in the definitions of terms such as health, pain, what is appropriate to disclose and to whom, what is considered to be rewarding, etc.

A final methodological consideration in cross-cultural research should be the range of topics covered under ethical considerations, usually governed in the United States by institutional review boards, and which also have been developed internationally (e.g., Nuremberg, Helsinki accords, etc.). Institutional Review Boards or Ethics Committees have strict guidelines for determining appropriate compensation for participant time, informed consent,

determination of procedures to guard against any coerciveness in participation, etc. These standards are often more restrictive for child research participants than for adult subjects.

### **1.5 Statistical analyses and reporting of results**

The demographic 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:

- Literacy, native language and whether it is the dominant language of the country,
- Religious affiliation,
- Proportion of subjects who were educated abroad (communication from working team members),
- Use of “traditional” vs. western providers for health care.

Other potential confounders that should be considered are listed in the section on “Guidelines for documenting potential confounders.” Elsewhere we recommended detailed characterization of samples using templates; these may be too lengthy to include in the main journal article but could be published as supplemental material on the journal’s website.

**Table 1. Diagnostic questionnaires, severity scales, and quality of life scales**

Abbreviation	Full name	Type	Languages	Reference
R3DQ	Rome III Diagnostic Questionnaire	Diagnostic criteria for all FGIDs	Chinese, Japanese, Spanish, Korean, Italian, Portuguese, Romanian, Hebrew, et al.	(30)
BDQ	Bowel Disease Questionnaire	Identification of FGIDs	?	(31)
FBDSI	Functional Bowel Disease Severity Index	Disease-specific illness severity index	?	(32, 33)
IBS-SSS	IBS-Symptom Severity Scale	Disease-specific illness severity index	Japanese, Spanish	(34)
FICA	Fecal Incontinence and Constipation Assessment	Disease-specific severity scales	?	(35)
FISI	Fecal Incontinence Severity Index	Disease specific severity scale	?	(36)
PAC-SYM	Patient Assessment of Constipation	Disease-specific severity index	Spanish	(37)
SF-36	Short Form-36	Generic HRQOL	Japanese	(38)
SIP	Symptom Impact Profile	Generic HRQOL	?	(39)
EurQol	Generic HRQOL	Generic HRQOL	?	(40)
IBS-QOL	IBS-Quality of Life	Disease-specific HRQOL	Chinese, Japanese, Korean, Iranian, Spanish, Romanian, et al.	(41)
IBSQOL	IBS Quality of Life	Disease-specific HRQOL	?	(42)
PAC-QOL	Patient Assessment of Constipation: Quality of Life	Disease Specific HRQOL	?	(43)
GDSS	Glasgow Dyspepsia Severity Scale	Disease-specific severity index	Spanish	(44)
SODA	Severity of dyspepsia assessment	Disease-specific severity index	Spanish	(45)
LDQ-SF	Leeds dyspepsia questionnaire-short form	Disease-specific severity index	Spanish	(46)
SLDQ	Spanish language dyspepsia questionnaire	Disease-specific severity index	Spanish	(47)

Abbreviation	Full name	Type	Languages	Reference
PAGI-SYM	Patient assessment of GI disorders symptoms	Disease-specific severity index	Spanish	(48)
PAGI-QOL	Assessment of upper GI disorders-quality of life	Disease Specific HRQOL	Spanish	(49)
NDI	Nepean dyspepsia index	Disease-specific severity index	Spanish	(50)
FDDQL	QOL questionnaire for FGIDs	Disease Specific HRQOL	French, Spanish	(51)
GCSI	Gastroparesis cardinal symptom index	Disease Specific severity index	Spanish	(52)
GSRS	GI symptom rating scale-original interviewer-administered version	Disease Specific severity index	Swedish, Spanish, Japanese	(53)
RDQ	Reflux disease questionnaire	Disease Specific severity index	Spanish	(54)
GIQLI	Gastrointestinal quality of life index	Disease Specific HRQOL	Spanish	(55)

**Table 2: Psychological scales for use in cross-cultural studies**

Abbreviation	Full name	Type	Languages	References
BSI-18	Brief Symptom Inventory	Anxiety, Depression, & Somatization	Japanese	
HAD	Hospital Anxiety & Depression	Anxiety & Depression	Spanish	(56)
PHQ-15	Patient Health Questionnaire-15	Somatization	Japanese	
RPSQ	Recent Physical Symptoms Questionnaire	Somatization	Japanese	(57)
CMCQ	Comorbid Medical Conditions Questionnaire	Somatization (comorbidity)	Japanese	
CSQ	Coping strategies questionnaire	Cognitive coping scale	Spanish (Spain)	(58)
VSI	Visceral Sensitivity Index	Gut-specific anxiety	Japanese, Hebrew	(59)
DHSI	Digestive Health Status Instrument		?	(60)
CS-FBD		Disease-specific cognition scale	?	(61)
SOC	Sense of Coherence	Coping skills	?	(62, 63)

**Table 3. Points of contention relating to cross-cultural differences in symptom reporting of bloating, distension, and fullness.**

Point of contention	Current paradigm	Socio-cultural issues	Research questions
<b>Bloating is a universal term used to describe a common symptom of IBS.</b>	Bloating is used to describe a sensation of increased pressure within the abdomen, with or without visible increase in abdominal girth.	The origin of the word suggests that bloating can also be used to describe 'soft and flabby,' as in a 'bloated bureaucracy'. In fact the word bloating is non-existent outside of English. In Latin and Indian languages, distension and swelling are used, but the most common description is inflammation. In Italian, a Latin language, patients do not use "distensione" but Gonfiore (noun) and the usual expression is "I feel gonfio (inflated and tense)". In Chinese composite terms have been coined to accommodate this concept.	Should the word bloating be replaced by a more descriptive term differentiating a subjective sensation from a visible or objective distension? Would pictograms be more representative than textual items?
<b>Bloating is differentiated from distension; in the latter there is demonstrable increase in abdominal girth.</b>	Peter Whorwell has argued, based on limited evidence from two centers, that bloating tends to be associated with gas trapping, loose stools and visceral hypersensitivity, whereas distension tends to be associated with delayed transit and constipation (64).	Other languages do not generally differentiate between bloating and distension.	Should we describe distension as visible and non-visible? How much overlap is there in pathophysiological disturbances between those with and without visible distension?
<b>Fullness is differentiated from bloating based partly on the localization of the sensation to the upper or the lower abdomen respectively. However, overlap is common in Asia, including India. In the Indian and Chinese cultures, upper abdominal fullness after eating may be considered as eating an adequate amount food rather than symptom of a disease.</b>	In the Rome paradigm fullness is a symptom addressed in gastroduodenal disorders, while bloating is addressed as a bowel disorder.	In Chinese the word zhang can be used to describe either fullness or distension. 'Wei zhang' (literally gastric distension) is used to describe distension in the upper abdomen and by implication as the symptom equivalent of fullness. 'Du zhang' (literally distension centred in the navel) is assigned as the symptom equivalent of bloating. In Italian patients say I feel "pieno" (full) and are referring to the postprandial feeling of fullness, so this is a symptom of dyspepsia.	How well can patients, physicians and scientists differentiate between fullness and bloating? Are there studies that demonstrate localization of sensation to the upper or lower abdomen according to the site of gas infusion or visceral distension? Is this separation between upper and lower abdomen and between IBS and FD artificial?



Point of contention	Current paradigm	Socio-cultural issues	Research questions
<b>The sensation of distension or pressure in association with meals is described as dyspepsia, while its association with disordered defecation is described as bloating.</b>	Post-prandial fullness is defined as a symptom originating from the gastroduodenal region. Abdominal discomfort, possibly including bloating, that is relieved by defecation could be considered as a symptom of IBS.	In Chinese history and culture “the common people regard food as Heaven” (old Chinese proverb). All food is believed to have medicinal value, and health is maintained by selecting foods to match the individual’s constitution. In Chinese, one “eats medicines” rather than “takes medicines” and in ancient times, court chefs were considered to be physicians.	Can this primacy of nutrition in Chinese society create a preferential labelling as a disorder of digestion as opposed to defecation? Will a precise timing of the onset of the distension sensation enable us to ascertain the origin of the stimulus? Can colonic motor activity associated with a gastro-colonic reflex be related to bloating or fullness sensations?
<b>Bloating and abdominal pain are related but distinct manifestations of gastrointestinal disturbances.</b>	Western cultures appear to conceptualize pain and bloating as related concomitants of gastrointestinal disturbance. Gerson et al. (65) observed significant positive correlations between pain and bloating in 7 of 8 countries.	The only exception in the Gerson study was in China where this relationship was significantly negative. An explanation that has been suggested is that in China the two symptoms may be conceptualized as being on a continuum where bloating may be a milder form of pain, so they do not co-exist and are negatively correlated.	What are the socio-cultural factors operating in different societies that influence preferential labelling of aversive sensations as painful or non-painful?

## **Section 2. Fostering Research Networks and Multinational Research Collaboration in FGIDs**

### *Sub-committee chair:*

**Kok Ann Gwee MD, PhD, Singapore**

### *Working team members:*

**Enrico Corazziari, MD, Italy; Shin Fukudo, MD, PhD, Japan; Charles Gerson MD, USA;**

**Uday C. Ghoshal, MD, DM, India; Rona L. Levy, MSW, PhD, MPH, USA;**

**Max Schmulson MD; Mexico; Ami D. Sperber MD, MSPH, Israel;**

**William Whitehead PhD, USA**

### *Working team consultants:*

**Mary-Joan Gerson PhD, USA; Chen Minhu MD, PhD, China;**

**Seung-Jae Myung MD, PhD, South Korea; Eamonn Quigley MD, Ireland/USA;**

**Peter Whorwell, MD, UK; Katie Zarzar, USA**

This section describes the potential for developing research networks and collaborations across countries, and across agencies and companies. We provide some examples of research questions that highlight the potential impact of cross-cultural issues. We suggest how these multi-national networks may be organized in terms of infrastructure, administration, and communication. We propose a series of recommendations to guide the development of multinational, cross-cultural research.

The section consists broadly of two parts:

- Recommendations for the development of multi-national research networks.
- Potential research areas with examples of specific study proposals involving cross-cultural issues that could benefit from multi-national collaboration.

For greater detail the reader is referred to the appendices in which each subject is addressed in full.

## 2.1 Guidance for developing multi-national research networks

Appendix 2 presents a compendium of existing or planned multinational networks and projects for research in the FGIDs.

### Recommendation #8

- *The list of existing networks should be published on the Rome Foundation website where a dedicated link to multinational FGID research will be established.*
- *Dissemination of information and communication among potential collaborators can be attained through:*
  - *The Rome Foundation mailing list.*
  - *The Rome Foundation website.*
  - *The Rome Foundation International Liaison Committee (ILC).*
  - *The World Gastroenterology Organization through member societies, the WGO website, and WGO e-mail communications.*

### 2.1.1 Conditions for fostering research networks

It may be difficult for individuals who have grown up in one culture to evaluate critically

how it may differ from others. Thus, a prerequisite for positive engagement in multinational collaborative research is a commitment to seeking to understand other cultures, an openness to exploring differences between them, and an interest in how they may impact on health and disease.

A common language is an advantage in multi-national collaboration. However, where the research question seeks to understand the effect of cultural factors in different societies, it is inevitable that study protocols will have to cater to different languages. For example, in Asia there are primary languages some of which have multiple variants. While English can be used as a common language, it is important to have a good balance with equal input from each cultural group involved. A key is to avoid submersion of non-English cultures. On the one hand, diagnostic criteria and clinical questionnaires must be standardized to allow for comparison. On the other hand, it is important to keep in mind that what may appear in one culture to be a minor or nuanced change in wording may have profound effects on understanding of the disorder or symptom experience in a different setting.

### 2.1.2 Organization of networks: infrastructure, administration, and communication

Communication among project members is of the utmost importance. There are many ways to accomplish this.

#### 2.1.2.1 Conference calls (including video-conferencing)

The conduct of conference calls offers obvious advantages for international collaboration. However, culturally speaking, these faceless conferences have inherent limitations in that some cultural groups may have inhibitions about speaking out of turn, the effect of which is that one or several individuals may dominate the call, even when unintended, while others do not speak out. Thus, it is still important to have periodic face-to-face meetings. The principal investigator should make it clear at the outset that all members must commit to these meetings.

#### 2.1.2.2 Email

It is important to keep all investigators fully informed. A good way to accomplish this is to

set up an email group and routinely copy all investigators on all communications related to the study. To avoid misunderstanding, abbreviations should be avoided in all correspondence.

### **2.1.2.3 Internet**

There are ever-increasing means to communicate and collaborate through the Internet including social media and specific websites that facilitate sharing of material and editing of documents in an on-going process. The Rome Foundation, for example, is conducting its projects through the BaseCamp web-based system. In addition, the Internet can be used to conduct surveys, establish and manage databases, and conduct statistical analyses. All these means can be harnessed to the work of research networks and collaborations. Academic institutes and commercial companies are offering consultation on and/or help in the conduct of Internet-based research and journals on Internet research are available. An example of the latter is the Journal of Medical Internet Research (JMIR; [www.jmir.org](http://www.jmir.org))

### **2.1.3 Identifying funding sources and collaborators**

*(Appendix 3: Inter-agency collaboration)*

National research agencies rarely support cross-cultural research, although regional societies are known to support multi-national research where the majority of participating countries are from the same region. Pharmaceutical companies appear to be the most frequent supporters of multi-national studies, although there are international agencies that can be approached for support.

Some conditions should be adhered to when fostering collaboration with other organizations, pharmaceutical companies and regulatory agencies. It is imperative to have a strong and sound framework to avoid misunderstandings. This is particularly important for clinical trials.

One should distinguish among three categories of relationships:

- Agreements with agencies or foundations (these most often take the form of grant applications).
- Agreements with one or more pharmaceutical companies to carry out an investigator-initiated research study.

- Agreements with one pharmaceutical company to carry out a clinical trial (in which there may be multiple performance sites).

### **Recommendation #9**

- *Research agreements with companies and/or agencies should clearly state:*
  - *The aims of the study.*
  - *Who owns the data and can conduct analyses?*
  - *Who has the right to publish the data and who are the study authors?*

In the first category (grants from foundations and agencies) there is usually no question of conflict of interest.

In the second category (investigator-initiated studies) the question of conflict of interest quickly arises and the best means of protection for academic investigators is to seek multiple sponsors, to avoid confidentiality agreements, and to insist that the data provided by industry should be in the public domain.

### **2.1.4 Logistic barriers**

The regulatory and logistic barriers to sending biological samples and testing pharmacological agents impose limits to the range of studies that are amenable to multi-national collaboration. While there is the possibility of using local facilities to process test samples, before pooling the data electronically for analysis, this approach imposes its own set of challenges not least of which is ensuring rigorous standardization of processes and equipment. It should be noted that many of these barriers can be overcome with modern technology and this process will only improve over time.

Obviously, questionnaire-based studies are the easiest to conduct.

### **2.1.5 Potential research areas for cross-cultural research in the FGIDs**

The FGIDs represent a broad canvas for potential areas of research interest. In this section we present several examples of subjects that could be addressed in research projects. We have focused on three areas of interest:

- The challenge of culture and language in the subjective reporting of fullness, bloating, and distension.

- A comparison of healthcare services in four countries and their influence on diagnosis and care for FGID patients.
- Cross-cultural multinational research into intra-family illness behavior dynamics.

The first two are summarized in this section and presented in detail in Appendices 4 and 5, respectively. The third is presented in Appendix 6 in abstract form.

The following were sources of information for this section:

- The WGO provided insight into global perspectives.
- Members of existing multi-national research projects within geographical regional groupings in Europe, Asia, and Latin America, and inter-continental projects between the US and Japan.
- Academicians in the fields of medical anthropology, psychology and behavioral medicine.

We applied the following criteria to identify research proposals that might be prioritized:

- The study could benefit from multi-national collaboration, preferably across different continents and regions.
- The study assesses the effect of various factors on the etiology and course of FGIDs, e.g., stress and other sources of psychological trauma, diet, hygiene, and health care delivery systems.
- Where possible the study seeks to test the validity, applicability and/or utility of the Rome diagnostic criteria in different cultures and languages.
- The study contributes to advancing knowledge in outcome assessment or trial design in FGID treatment trials.
- The aims should be feasible to implement and likely to attract funding.

Other potential research areas that could benefit from multi-national cross culture collaboration, but are not focused on in this report include:

- Psychopathology and somatization in different cultures and regions.
- Attribution of symptoms (mind-body).
- Food- and eating-related symptoms.
- IBS phenotype (sub-types) – universal or different?

#### ***2.1.5.1 Project - The challenge of language in the subjective reporting of fullness, bloating and distension***

(Appendix 4)

This project collated the actual words or equivalent terms used to describe bloating in major languages such as English, Chinese, Hindi, Italian and Spanish, how these terms are perceived and what they imply in the respective cultures. We identified a notable discrepancy between English and the other languages; no other language had a distinct term for bloating as opposed to distension, whereas all languages had an equivalent term to distension. We obtained feedback on how to resolve this discrepancy – recommendations that included the use of pictorial or diagrammatic representations in different cultures and use of either the terms ‘swelling’ or ‘distension’ or ‘inflammation’ with qualification on whether these were visible or not.

We noted that in Chinese the same word is used to describe fullness and distension, and this could be a factor in the misdiagnosis of IBS as an upper GI condition. We also noted that in some cultures the term bloating may be used as a surrogate for discomfort, with the possibility that IBS may be underestimated if it is classified as a non-specific functional bowel disorder or functional bloating.

#### **Recommendation #10**

- *Defining the influence of culture and language on how we interpret and assign the origin of symptoms and complaints should be a priority research area.*

#### **Action point #4**

- *A Rome Foundation committee should further define the utility and place of pictograms in cross-cultural research.*
- *This might be best accomplished by a cross-cultural research project aimed at assessing the relative value of text and pictogram questionnaire items.*

### **2.1.5.2 Project - Comparison of the health care infrastructure in South Korea, India, Italy, and Mexico**

(Appendix 5)

This project describes the healthcare infrastructure and provisions in different countries, and examines how these may impact on health seeking behavior by subjects with IBS, and on treatment approaches by physicians treating this condition. At the same time, the findings also show that disease epidemiology and cultural familiarity and acceptance of western and complementary-alternative medicine in these countries may have confounding effects on IBS healthcare seeking and treatment behaviors on both sides of the consultation table. The report contains a large body of information, but understandably, direct and IBS-specific information is limited. Therefore, only broad observations are possible and it is acknowledged that interpretation is based to a large extent on our experts' personal perspectives of the systems and it is not always possible to provide documentary support. The results of this survey highlight the importance of the issue and the need for future research on it.

South Korea has an efficient national health insurance system that provides universal coverage at a very advanced level of care for IBS patients. Of particular interest is the high level of evaluation by endoscopy procedures with over 50% having had colonoscopy. Interestingly, over 50% of IBS patients have also had upper GI endoscopy, suggesting the possibility that there is a high level of overlap with dyspepsia, and/or in view of the high prevalence of *Helicobacter pylori* in this population, a greater concern for upper GI diseases. On the other hand, in Mexico, where the social security systems are not as well funded patients, even in tertiary care centers, primarily undergo inexpensive blood tests repeatedly. Furthermore, in Italy and Mexico the state-regulated system appears to impose restrictions on access to hospital-based services, which may include endoscopy, although in Mexico these services may be available through private practice. In India while there is open access to all levels of the healthcare system, the uptake of endoscopic procedures does not appear to be as substantial as in Korea. Possible reasons may include the level of hospital

funding and manpower support, the size of the population and the its rural spread.

With respect to medications, a wide range of pro-kinetic and anti-spasmodic agents are available in all four countries, in contradistinction to the US. It is noteworthy that Rifaximin is available in all four countries. In South Korea anti-depressants can only be prescribed to IBS patients if a psychiatric diagnosis is made, while in Mexico all classes of anti-depressants can be prescribed for the treatment of IBS.

### **2.1.5.3 A study of intra-family illness behavior dynamics in different cultures (Appendix 5).**

The way families interact in response to illness has an important impact on the clinical pattern of many diseases. For IBS, with its reported association between psychosocial factors and health seeking behavior, it is proposed that knowledge gained from studying intra-family illness behavior dynamics can be applied to improving our understanding of the disorder and our management skills. Even more exciting is the possibility of contributing to developing strategies to prevent the development of IBS. For example, functional abdominal pain in childhood has been shown to be a precursor to functional GI problems in adulthood. However, while a significant body of literature exists in the United States that links specific parental cognitions and behaviors with the development and maintenance of abdominal pain in children, attempts to replicate these findings in Japan have led to contrary findings. Another example of a discrepancy between different cultures is the significant differences on the IBS Mind-Body Belief Scale observed in two Asian countries in particular compared with Westernized societies (12).

These observations highlight the limitations of psychological and behavioral studies involving single population or culturally homogenous societies. They also further highlight the importance of ensuring that translations should be culturally adapted rather than literal.

## ***Appendix 1. Translation and validation of study instruments***

***Ami D. Sperber and Katie Zarzar***

The need for the translation of study material into different languages is steadily increasing and has become a cornerstone of modern research (16). However, cross-cultural translation has pitfalls that threaten validity. Some of these pitfalls are difficult to detect unless a rigorous and standardized methodological process is adopted. Failing to do this could have unrecognized, deleterious effect on study results (17). Thus, flawed methodology may lead to erroneous research conclusions, which, although due to technical flaws, are undetectable as such and considered to be substantive in nature.

The translation of many terms is not straightforward, since there are potential cultural differences in their interpretation. For example, a seemingly simple term such as “family” may be interpreted differently in various cultures. In some cultures family may refer primarily to first-degree relatives, while in others the interpretation may be much broader. Female and male are universal concepts, but the closely related terms femininity and masculinity may be interpreted very differently in some cultures (18).

Even within the same language, various terms may be used for the same concept in different dialects, in different geographical regions or among cultural sub-groups. For example, in a study of the epidemiology of irritable bowel syndrome (IBS) among Israeli Bedouin Arabs (6), the Rome II questionnaire was translated into Arabic by a professional translation company that specialized in translating into Arabic. Bedouin physicians from the region in which the study was to be conducted were asked to go over the final Arabic version of the questionnaire. They pointed out that the Arabic term used for “bowel movement” was in common use among Israeli Arabs, but would not be understood by the majority of Israeli Bedouin Arabs who use another term. The non-Bedouin native Arabic speakers who did the original translation were not aware of this fine point. Thus, without this additional validation step the study participants would not have understood a central study concept and the results would have been flawed.

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) and is culturally relevant and comprehensible for the target culture (66). Thus, the aim is to achieve a “conceptually equivalent” rather than a “literal” translation. To this end advanced planning is essential (19-21) so that the dual processes of translation and adaptation will be as effective as possible. 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.

### ***Guidelines for translation and adaptation of questionnaires***

There are two alternative starting points for multinational, cross-cultural research. In the first a research instrument is developed *de novo* for use in two or more languages and can be molded in an ongoing reciprocal process. An assumption underlying this approach is that neither language is primary (no source language). It allows for greater creativity and provides the opportunity to align the two versions more closely. However, this process is extremely resource consuming and often impractical given the circumstances under which most multinational, cross-cultural studies are conducted.

In the second condition an existing questionnaire (most often English) is chosen for use in a different “target” ethnic and language group and has to be translated into the target language. The translation process requires skill, knowledge and experience. There are critical translation problems that adversely affect many studies, even with professional translators (19). Some translators are not sufficiently aware of the rigorous requirements of translation for cross-cultural research. They may spend too much time on literal translation, without devoting enough attention to cultural nuances. Colloquial phrases, slang and jargon, idiomatic expressions and emotionally evocative terms may be particularly difficult to handle.

Because of the growing importance of translation for international studies, several developments have taken place over recent decades. These include:

- An increasing understanding of the need to anticipate potential difficulties in translation when developing new

questionnaires (23). This process, known as “translatability assessment,” is discussed below.

- The efforts of the FDA and other regulatory agencies to make the development and translation of PROs a process (22).
- The work of multinational professional societies and associations dedicated to the refinement of research methods, particularly in the area of outcomes research.

These organizations have published guidelines relating to cross-cultural translation, translatability assessment, and migration from PROs to e-PROs, as discussed below. Examples of this are the European Organization for Research and Treatment of Cancer (EORTC), which has developed quality of life instruments and carefully monitored their translation into multiple languages, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) have published relevant translation and migration guidelines (23-25).

There is an increasing presence and importance of commercial companies that specialize in the translation of research instruments for multinational studies. The translation process adopted and recommended by most associations and commercial translation companies today are similar in structure and content and usually include some variation of the following 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.romecriteria.org/translations>.

In general terms the following process is used (Fig. 1):

1. Two translators who are fluent in the source language and native speakers of the target language independently perform forward translations with the aim of maintaining conceptual equivalence to the source language while keeping in mind the need for cultural appropriateness for the target country. This step produces two versions in the target language.
2. A third independent linguist whose native language is the target language compares the two forward translations and tries to bridge any significant differences to produce a unified, reconciled translation. The final product of this step is a single translation in the target language. A recent study looked more closely into this

reconciliation step and formulated criteria for its implementation (67).

3. A linguist whose native language is the source language then translates the reconciled document back into the source language using only the reconciled final forward translation as source material.
4. The new source language version produced in step 3 is compared by a bilingual linguist with the aim of resolving any discrepancies between the original version and the back translation produced in step 3, which are both in the source language and making changes, if indicated, in the final target language version.
5. A clinician who practices in the relevant medical area and is a native speaker of the target language either accompanies the process through the first 4 steps to provide feedback from a clinician’s point of view, or does so at this stage based on the target language version produced in step 4. Following discussion between the linguist and the clinician as to any changes that the clinician deems necessary, the final target language instrument is produced.
6. Qualitative interviews are conducted with 5-10 pre-screened respondents who are representative of the study’s target population to provide cognitive feedback on the linguistic and cultural appropriateness of the target language instrument resulting from step 5. Any final changes are made to the target language version based on these interviews.
7. The finalized target version is proof-read by a linguist who is a native speaker of the target language.
8. The final version of the instrument in the target language is approved for use.

### ***Translatability Assessment***

Translatability assessment is a recently developed process aimed at identifying potential translation and adaptation problems in the initial instrument development stage in the source language. Instruments are often developed for immediate use in the local target population without consideration for future global application. Conducting a translatability assessment during the instrument development stage prevents challenges in concept adaptation and equivalency when instruments are later translated for use in global studies.

There are multiple methodologies for completing a translatability assessment. Two of



the most common methodologies include the review of the English source questionnaire by a linguistic validation expert, and the second option involves the review by a linguistic validation expert and a review by linguists.

In the first methodology, the linguistic validation expert identifies text or concepts that may present difficulty in translation, or impede the development of conceptually equivalent language versions in future translation efforts, with particular focus on languages known to be more problematic. Consultation with linguists may also take place, but will not include a per language in-depth analysis by individual linguists.

The second option involves the review of the English source questionnaire by a linguistic validation expert, as well as a linguist per target language to review the source English questionnaire. The linguistic validation experts and linguists identify text or concepts that may present difficulty in translation, or impede the development of conceptually equivalent language versions in future translation efforts. As with the first option, there is particular focus on languages known to be more problematic. Each linguist provides in-depth analysis of potential challenges for their particular language pair, and the linguistic validation expert then synthesizes this information into a report documenting the findings of this review, and detailing suggestions for modifications to the English source.

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. While not every cultural and linguistic challenge can be eliminated via translatability assessment, many can be prevented via the selection of alternative options or the removal of items that are too culturally specific to be effectively adapted.

### ***Translation and validation of endpoints***

The translation of trial endpoints can be problematic due to the language present in the source (English) questionnaire to be translated. Due to the critical nature of the data gathered by endpoints supporting labelling claims, it is essential that these risks are mitigated via a translatability assessment.

The translation of endpoints bears a more significant weight than translation of other more general documents in a trial due to the critical role of primary and secondary endpoints in a

trial. 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. As with literal translation, translation and cultural adaptation (linguistic validation) of instruments face challenges resulting from linguistic and cultural differences across target countries. These challenges and differences in language, if not appropriately managed, can directly impact the validity of the data gathered in a global clinical trial.

The importance of defining each item's conceptual meaning is the most critical step in mitigating this risk. By defining in detail each item's intended meaning, listing approved synonyms, and listing terms or descriptors that would detract from the item's intended meaning, we can provide the linguists with the specific guidance necessary to develop conceptually equivalent content in the target language version. Immediately following concept definitions, the selection of appropriate translation partners, linguists, clinician consultants, and cognitive interviewers to conduct the qualitative patient interviews with respondents in each target country is vital to mitigating the risk involved in translation and cultural adaptation of endpoints. These experts 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.

### ***Migration of PROs to e-PROs – measurement equivalence***

Patient-reported outcome (PRO) data are collected directly from patients. PROs are often used to measure treatment efficacy in clinical trials, and may serve as primary or secondary end-points. To date, PRO data have typically been collected using paper-and-pencil measures. However, electronically administered PRO measures (ePROs) are increasingly being used (26). Understandably, there was uncertainty regarding the "migration" of PROs to the electronic environment and studies have been conducted to evaluate the process and formulated guidelines for future practice (24, 28). This is particularly important in light of the interest expressed in this issue by the FDA and other regulatory agencies (22).

One meta-analysis synthesized 65 studies that directly assessed the equivalence of computer versus paper versions of PROs used in clinical trials. A total of 46 unique studies,

evaluating 278 scales, provided sufficient detail to allow quantitative analysis. The investigators found that extensive evidence indicates that paper- and computer-administered PROs are equivalent and that validation studies should not generally be required when migrating a PRO measure from paper to computer, although cognitive interviewing may be useful to ensure that patients are interpreting the migrated or reformatted items in the intended manner (26).

Another study into the comparability of PROs and ePROs, conducted by the ISPOR's ePRO Good Research Practices Task Force, generated a general framework for decisions regarding the level of evidence needed to support modifications that are made to PRO measures when they are migrated from paper to ePRO devices in the hope that the good research practice recommendations would provide a path forward for researchers interested in migrating PRO measures to electronic data collection platforms.

## ***Appendix 2. Existing Multi-national FGID Research Networks***

***William Whitehead, Kok Ann Gwee, Max Schmulson, Enrico Corazziari***

The following is a list of multinational research networks known to the committee members that focus on FGIDs. Included with each is a brief description provided by the organizers, an indication of whether the network is open to new proposals and new investigators, and contact information. This list is not exhaustive; there may be other research networks.

- **Rome Foundation Asian Working Team.**

This working team is jointly sponsored by the Asian Neurogastroenterology and Motility Association and the Rome Foundation, and it is chaired by Kok Ann Gwee and co-chaired by Bill Whitehead. Members of the steering committee include central FGID experts from India, China, Thailand, Malaysia, Japan, Taiwan, Korea and Singapore. Recent additions to the consortium include the Philippines and Indonesia. The goal of this working team is to determine whether the presentation of symptoms by Asian patients diagnosed with FGIDs is consistent with the Rome criteria and is similar to FGID patients in North America and Europe. This is being addressed by adding questions to the Rome Diagnostic Questionnaire, translating and validating this questionnaire in each country's language, and carrying out a survey of clinic patients with FGIDs in each country. This network is open to new proposals. Contact is Kok Ann MD, email address [slbclinic@gmail.com](mailto:slbclinic@gmail.com).

- **Central America-Mexico-South America and Spain Consortium.** This group is led by Douglas Morgan and Max Schmulson. Fermin Mearin and Enrique Rey are collaborators from Spain. The original impetus was to survey FGIDs in Latin America and Spain, and investigate the impact of war and other stresses on prevalence. An additional task is the translation of the Rome II and III Diagnostic Questionnaires. Several full papers and abstracts have been published. This network is open to new proposals. Contacts are Douglas MD, [douglas\\_morgan@med.unc.edu](mailto:douglas_morgan@med.unc.edu); and Max J. Schmulson at [maxjulio@prodigy.net.mx](mailto:maxjulio@prodigy.net.mx).

- **Latin-American Network through the Sociedad Latinoamericana de Neurogastroenterología (Latin American Society of Neurogastroenterology).** This group includes Max Schmulson and Aurelio López-Colombo from Mexico, Carlos Francisconi from Brazil, Ana María Madrid and Claudia De Filippi from Chile, Cesar Louis-Venezuela, Laura Solé, Pepe Tawil, and Luis Bustos from Argentina, Carolina Olano and Beatriz Iade from Uruguay, Rodolfo Peña, Edgar Pena, and Loreto Cortes from Nicaragua, and Isaac Quintero from Panamá. The original goal was to study bloating in the region, but it is now open to ideas for new projects. Contact is Max Schmulson, MD, at email address [maxjulio@prodigy.net.mx](mailto:maxjulio@prodigy.net.mx).
- **Mexico and El Paso-TX.** Marc Zuckerman of El Paso, Texas and Max Schmulson from Mexico lead this group. Currently they are studying differences in FGIDs between Mexicans from Mexico and Mexicans from El Paso. This network is open to new proposals. Contact is Marc Zuckerman, MD, at email address [marc.zuckerman@ttuhsc.edu](mailto:marc.zuckerman@ttuhsc.edu).
- **Gersons' Cross-Cultural Studies.** Mary-Joan and Charles Gerson have conducted several international cross-cultural investigations of patients with IBS. Their studies have spanned the globe, with collaborators in the US, Canada, Mexico, England, Italy, Romania, Israel, Iran, India and China. Their studies have focused on psycho-social variables, with a particular focus on family relationships and mind-body attributions, as well as attachment style, catastrophizing and negative pain beliefs. An international study of attachment style, beliefs and IBS severity is currently being conducted with the participation of researchers from New York and Los Angeles (US), Italy, Romania, Iran, India, China, and Mexico. Open to new proposals. Contacts are Charles Gerson, MD, and Joan Gerson, PhD, at email address [cgeron@yahoo.com](mailto:cgeron@yahoo.com).
- **Japanese-U.S. Cross-Cultural Working Team.** The chairs of this group are Motoyori Kanazawa and William Whitehead. Other investigators are Shin Fukudo, Rona Levy, Olafur Palsson, and Doug Drossman. The primary project has been to compare IBS patients in Japan to those in the U.S. with

respect to symptom presentation and usual medical care for IBS. A second project compared mothers with IBS and their children in Japan to those in the US with respect to social responses to pain behavior.

Accomplishments have included the translation and validation of a number of frequently used psychological and GI symptom scales into Japanese. Open to new proposals. Contact is Shin Fukudo, MD, PhD, or Motoyori Kanazawa, MD, PhD, at email address [sfukudo@med.tohoku.ac.jp](mailto:sfukudo@med.tohoku.ac.jp) or [m-kanazawa@med.tohoku.ac.jp](mailto:m-kanazawa@med.tohoku.ac.jp).

- **Mediterranean Research Consortium.** This research network is led by Enrico Corazziari. Its goals are to assess the epidemiology, diagnosis and treatment of FGIDs in different countries in this Mediterranean region. Preliminary data were reported in two abstracts that were submitted to pediatric GI Meetings. A similar initiative with greater participation of Eastern European Countries has been submitted for approval and sponsorship to the EUGF. Open to new proposals. Contact is Enrico Corazziari, MD, at email address [enrico.corazziari@uniroma1.it](mailto:enrico.corazziari@uniroma1.it).
- **GENIEUR.** This is a pan-European consortium whose purpose is to carry out well-powered studies of the genetic risk factors for IBS. Initial steps are the development of guidelines for recruitment and phenotyping. Contact is Beate Niesler, PhD, at email address [Beate.Niesler@med.uni-heidelberg.de](mailto:Beate.Niesler@med.uni-heidelberg.de).
- **WGO Initiative.** A study of immunohistochemical differences in IBS-C. Led by Carolina Olano from Uruguay and Greger Lindberg from Sweden and including Giovanni Barbara from Italy, Henry Cohen from Uruguay, Eamonn Quigley from Ireland, and Max Schmulson from Mexico. Open to new proposals. Contact is Eamonn Quigley, MD, at email address [equigley@tmhs.org](mailto:equigley@tmhs.org).
- 
- **Post-infectious IBS across Europe web-based survey.** This study, led by Robin Spiller, is a web-based survey for IBS patients to report the mode of onset and evolution of their IBS symptoms. Patients are informed of the study by their physicians and provided a

log on password. Supported by a grant from the United European Gastroenterology Federation. Contact is Robin Spiller, at email address [Robin.Spiller@nottingham.ac.uk](mailto:Robin.Spiller@nottingham.ac.uk).

- **The European Society for Primary Care Gastroenterology (ESPCG).** This society has representation from most European (and many Eastern European) countries. It maintains a membership list of 300+ and has affiliations, through its members with many academic departments of primary care across Europe. It was founded over 15 years ago and holds educational and research meetings, particularly at the world congress of primary care physicians (WONCA) and with the United European gastroenterology Federation (UEGF). The ESPCG has a formal committee structure and the current Chair is Professor Lars Agreus, head of the Centre for Family medicine at the Karolinska Institute in Stockholm. His e mail address is [Lars.agreus@ki.se](mailto:Lars.agreus@ki.se). The ESPCG receives financial support from the UEGF of which it is an affiliate member, and from the pharmaceutical industry through projects orientated resource and sponsorship. The ESPCG account is handled by Orbital Medic and the contact is Miss Kirsty Mousley at [Kirsty@orbitalmediapr.com](mailto:Kirsty@orbitalmediapr.com). The ESPCG makes a substantial contribution to the UEGF through membership of the its research committee (which plans the annual UEG Week) and by creating educational programmes which have been highly successful for on line use and have been used by the UEGF for commercial use (IBS) with the pharmaceutical industry. The website of the ESPCG is [www.espcg.eu](http://www.espcg.eu).

### ***Appendix 3. Identifying funding sources and potential collaborators for multinational research in FGIDs***

***William Whitehead, Eamonn Quigley, Kok Ann Gwee***

As a first step in identifying funding sources and collaborators for multinational studies, we examined published multinational studies of the prevalence of FGIDs to identify sources of funding. These are shown below. This list suggests that the US National Institutes of Health and other national research agencies rarely support cross-cultural research, and that pharmaceutical companies have been one of the most frequent supporters of such studies.

- Gerson CD, et al. Irritable bowel syndrome: an international study of symptoms in eight countries (65). **Supported by the non-profit Tai Foundation of New York.**
- Wald A, et al. A multinational survey of prevalence and patterns of laxative use among adults with self-defined constipation (68). **Supported by Boehringer-Ingelheim pharmaceutical company.**
- Talley NJ, et al. Gastrointestinal symptoms and subjects cluster into distinct upper and lower groupings in the community: a four nations study (69). **Supported by NH & MRC of Australia.**
- Hungin, APS, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects (4). **Supported by Novartis Pharmaceuticals.**
- Stanghellini V. Three-month prevalence rates of gastrointestinal symptoms and the influence of demographic factors: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST) (70). **Supported by Janssen Pharmaceuticals.**

#### ***Pharmaceutical companies***

Many large pharmaceutical companies are multi-national and many of them have carried out multi-national clinical trials (e.g., Novartis and Janssen). Some are willing to fund investigator-initiated studies. For example, Janssen and Abbott are both supporting the Rome Asian Working Team, which is carrying out a survey of FGIDs in several Asian countries under the leadership of Kok Ann Gwee and William Whitehead.

#### ***Regulatory agencies such as the US Food and Drug Administration***

These are unlikely to fund or collaborate on multi-national studies since their interests are national. However, it is possible that in multi-

racial or multi-ethnic countries, regulatory agencies may encourage or support studies of health care disparities or of racial and ethnic differences in drug tolerance or drug response.

#### ***International Liaison groups***

Rome International Liaison Committee (RF-ILC). This and similar groups are good places to look for collaborators but rarely have the ability to provide financial support.

#### ***Foundations***

- Large foundations such as the Gates Foundation often identify international studies as a funding priority. However, they prefer to fund intervention studies rather than prevalence studies.
- Quasi-federal foundations such as the U.S.-Israel Binational Foundation are possible funders of cross-cultural observational studies.
- The Rome Foundation awards small research grants (\$50,000) each year that have often gone to support multi-national prevalence and epidemiological studies for FGIDs. One of the priorities for review of grant applications is the conduct of multi-national surveys of FGID prevalence.
- International Foundation for Functional Gastrointestinal Disorders ([www.iffgd.org](http://www.iffgd.org); abbreviation IFFGD) is primarily a patient advocacy organization for patients with FGIDs and fecal incontinence. In addition to patient education, it sponsors a biannual meeting for professional education and awards a small number of research grants each year. Cross-cultural research studies would be eligible for these grants.
- The World Gastroenterology Organization Foundation (WGOF) ([www.wgofoundation.org](http://www.wgofoundation.org)) raises funds to support the World Gastroenterology Foundation (see below).

### **Professional Organizations**

*The World Gastroenterology Organization* ([www.worldgastroenterology.org](http://www.worldgastroenterology.org); abbreviation WGO) is a federation of 110 national societies and 4 regional associations of gastroenterology. Its focus is on sponsoring educational programs to disseminate best practices in clinical care, prevention, and research methodology. It does not offer funding for multinational prevalence studies but promotes awareness among the health care professions as well as the general public on global aspects of digestive health. It does provide assistance with the development of research projects

[www.worldgastroenterology.org/research-methodology.html](http://www.worldgastroenterology.org/research-methodology.html). Through the World Digestive Health Day (WDHD) and related activities, such as guidelines and educational symposia, WGO has addressed global aspects of irritable bowel syndrome (3) and common gastrointestinal symptoms, such as heartburn, dyspepsia, bloating and constipation.

- The American College of Gastroenterology ([www.gi.org](http://www.gi.org); abbreviation ACG) supports the clinical practice of gastroenterology in North America. It distributes over \$12 million annually in awards for clinical research and career development. Although cross-cultural research is not a program emphasis, this would fall within the scope of ACG. The ACG currently supports awards for International Trainees to spend time in the US and for US trainees to spend time overseas.
- American Gastroenterological Association ([www.gastro.org](http://www.gastro.org); abbreviation AGA) supports career development awards plus awards for specific types of research designated by contributors. Approximately \$1.5 million is awarded annually. Cross-cultural research is not a priority and research funding often goes to more basic science projects.
- The AGA has recently established its [AGA Researcher Directory](#). This directory is also open to non-AGA members. It is a tool for researchers to:
  - Identify potential collaborators.
  - Identify resources that may be shared among fellow researchers.
  - Identify potential mentors.
  - Indicate interest in participating in pharmaceutical or device clinical trials.
- American Neurogastroenterology and Motility Society ([www.motilitysociety.org](http://www.motilitysociety.org); abbreviation ANMS) provides professional education through an annual meeting, a

separate annual conference for clinical and research fellows, an annual course on how to perform and interpret clinical motility testing, and a fellowship program for month-long rotations in major academic GI Motility programs. The ANMS also awards two research grants each year, and cross-cultural research studies would be eligible. However, preference is given to basic or translational research proposals.

- The World Health Organization ([www.who.int](http://www.who.int); abbreviation WHO) is the agency responsible for health affairs for the United Nations. One of its missions is to collect health data and publish information on health status and health disparities throughout the world. However, it employs its own staff to gather this data and it does not provide grants to individual investigators.
- The Asian Neurogastroenterology & Motility Association ([www.asianmotility.org](http://www.asianmotility.org); abbreviation ANMA) is compiling translations of the Rome III questionnaire into 8 Asian languages, and plans to publish and make them available. The ANMA holds biennial scientific meeting, and periodic single topic meetings. Multi-national studies with the emphasis on clinical research, are promoted by encouraging member countries to jointly develop projects and to jointly approach a pharmaceutical or foundation sponsor.
- The European Society of Neurogastroenterology and Motility (ESNM), based in Vienna, [info@esnm.eu](mailto:info@esnm.eu) is similar to ANMS and ANMA and works together with them for international meetings and courses.

#### ***Appendix 4. Challenge of culture and language in symptom reporting: bloating, distension, and fullness.***

***Kok-Ann Gwee, Eamonn Quigley, Uday Ghoshal, Max Schmulson, Peter Whorwell, Minhu Chen***

##### ***Introduction***

“The dilemma with IBS is that its definition currently relies on symptoms alone and is, therefore, subject to the vagaries intrinsic to how patients express, and doctors interpret, complaints (71).”

How do we know whether a term employed by a patient to label his or her symptom is describing an identical or closely similar experience in other individuals? Does it truly matter? To address this question, language and culture-related issues and the potential influence that these exert on the interpretation of symptom reporting at the level of the patient-doctor communication and in FGID research, are reviewed in the context of bloating and its related terms, distension and fullness. The potential for overlap, miscommunication and inappropriate extrapolation were critically evaluated.

The findings of this review provide strong support that defining the influence of culture and language on how we interpret and assign the origin of symptoms and complaints should be a priority research area.

The language and cultural issues

- Bloating as an English term and distinguishing bloating from distension
- Are bloating and abdominal pain part of a severity continuum?
- Post-prandial fullness vs. bloating

##### ***Bloating as an English term***

The definitions given for the word bloating in various English dictionaries were reviewed. Wikipedia describes: “Bloating is any abnormal general swelling, or increase in diameter of the abdominal area.” It then goes on to state that: “The most common symptom associated with bloating is a sensation that the abdomen is full or distended.” The Merriam-Webster dictionary describes bloated to mean very swollen, too full of liquid, gas, and food. The definition given by Collins dictionary for bloated is: “a swollen state caused especially by gas retention inside the body.” Oxford dictionary gives the meaning as: “swollen with fluid or gas; origin: late 17th century (in the sense ‘cause to swell’): from obsolete bloat ‘swollen, soft,’ perhaps from Old Norse blautr ‘soft, flabby.’”

Peter Whorwell points to evidence that different but overlapping pathophysiological mechanisms might be involved in bloating and distension. He has proposed that bloating should be used when there is a sensation of increased pressure within the abdomen, whereas distension should be used when there is a demonstrable increase in abdominal girth (64). However, putting this into practice is a major challenge, not least because the word bloating appears to be confined to English speaking cultures. We found that in Spain, Italy, Romania, India, and Latin America there is no equivalent word for bloating, and distension is usually employed. In Spain and in Latin America, swelling appears to be used as an equivalent for distension, but also appears to carry the connotation of inflammation.

In England, bloating is used frequently but not distension. Could this experience in England have influenced English investigators to propose the concept that distension is visible, whereas bloating is sensory? In China, the word “zhang” is used to describe a feeling of expansion or distension. The word has been adapted to represent fullness by prefixing the Chinese word for stomach or gastric “wei” such that it becomes “wei zhang” when the sensation is perceived in the upper abdomen. The word “du” (centered in the navel) is prefixed to “zhang” so that “du zhang” has come to represent bloating. Do we have evidence that patients and physicians are able to discriminate between the source of fullness and bloating/distension?

In general we agree with the nomenclature adopted by Max Schmulson in his studies; subjective abdominal distension (to represent bloating) and visible or objective abdominal distension. Eamonn Quigley has proposed the terms experienced swelling (to represent bloating) and observed swelling (to represent distension). However, representatives for the non-English speaking countries observed the following difficulties with the term swelling; in Mexico and Latin languages, swelling carries the connotation of inflammation, while in Chinese the word swelling is distinctly different from the word distension, and also carries a connotation akin to edema. Nevertheless, when conducting surveys among patients in Latin America and Spain, abdominal inflammation and abdominal swelling, respectively, are the expressions that need to be used in questionnaires, even though they have the connotation of true inflammation.



### ***Are bloating and abdominal discomfort and pain part of a severity continuum?***

Irritable bowel syndrome (IBS) is characterized by symptoms including abdominal pain, unpleasant viscerosensory sensations (such as bloating, fullness, or sensation of gas) and alterations in bowel habits. Although pain is a specific sensation, the subjective report of discomfort in patients with IBS can reflect a wide range of symptoms, including discomfort during bowel movements, sensations of bloating, fullness, incomplete evacuation, and urgency. Americans consider pain and discomfort on a continuum of severity, whereas Europeans consider them as different types of nociceptive input (72, 73). On the other hand, Western cultures appear to conceptualize pain and bloating as related concomitants of gastrointestinal disturbance. In a study by Gerson et al. significant positive correlations between pain and bloating were found across seven countries (65). The only exception was China where this relationship was significantly negative. An explanation that has been suggested is that in China the two symptoms may be conceptualized as being on a continuum where bloating may be a milder form of pain, so they do not coexist and are negatively correlated. Gerson's study also found that differences in symptom expression existed between different parts of Europe. Pain, discomfort and bloating scores were consistently higher in Italy than in England.

Here we should consider the potential influence of sociocultural norms and issues of language usage and symptom interpretation. Comparing Italian and Irish immigrants expressing facial pain, it was reported that the Irish minimized their description of pain, in effect denying it to others, whereas the Italians embellished it by reporting more symptoms in more bodily locations and more dysfunction with greater emotional expression (74). Is it possible that in some cultures patients may choose to describe mild pain or discomfort as distension? Do some patients perceive pain as indicating a more serious condition, and distension as indicating a dietary indiscretion?

### ***Post-prandial fullness vs. bloating***

There are data suggesting that in Chinese societies physicians and patients may be influenced by socio-cultural factors to attribute the origin of abdominal symptoms to a digestive problem in the upper GI in preference to a disorder of bowel function. In a study from Taipei, Taiwan, of patients initially diagnosed

with FD on Rome I criteria, 50% were found to actually have pure IBS, as their upper abdominal pain or discomfort was relieved with defecation (75). In a study from Guangzhou, China, post-prandial fullness was the only independent predictor of FD patients with IBS overlap in patients who fulfilled Rome III criteria for FD (76).

Kleinman et al. noted that in China communicating psychological distress can be stigmatizing (77). Thus, it would appear that in a society where nutrition is believed to be fundamental to the maintenance of health and there is a reticence to communicate psychological distress, the attribution of symptoms to dysfunctional digestive system could gain more ready acceptance. In Chinese medicine, diet plays a crucial part in any treatment program; indeed, the Chinese verbs for 'to eat' and 'to take' (medicine) are the same. All food is believed to have medicinal value. An old Chinese proverb says, "The common people regard food as Heaven" (min yi shi wei tian). Can this primacy of nutrition in Chinese society create a preferential labelling of aversive sensations as arising in relation to meals as opposed to a bowel dysfunction?

### ***Conclusions***

In this review and survey, we found that there is no consistent understanding of the term bloating across cultures and languages. It is interesting to note the success with which this word has been perpetuated by English-language authors, and how non-English scholars have adapted words from their own language to represent bloating. The distinction between bloating and fullness appears to be influenced by socio-cultural priorities. In Chinese societies the implications on digestion appear to be viewed with greater seriousness than the links to defecation, thus possibly favoring a diagnosis of dyspepsia over IBS. The findings of this review provide strong support that defining the influence of culture and language on how we interpret and assign the origin of symptoms and complaints is a priority research area. The key points of contention, current paradigms, sociocultural issues and our recommendations are summarized in Table 3 (above).



***Appendix 5. A Comparison of healthcare services among four countries and their implications for diagnosis and care of FGID patients***

***Max Schmulson, Enrico Corazziari, Uday Ghoshal, Seung-Jae Myung, Kok-Ann Gwee***

***Introduction***

When conducting cross-cultural research, several issues need to be taken into account in order to compare outcomes from different parts of the world. These include:

- The level of responsiveness of the healthcare services to the expectations of the population.
- The priorities that people in different cultural and social settings accord to various aspects of healthcare services.
- Differences in the availability of medicine.
- The contextual differences between health facilities, which may influence the application of diagnostic criteria and treatment algorithms.

The goal was to survey and describe healthcare issues that should be considered when conducting cross-cultural studies in FGIDs. The focus is on IBS, the most widely studied FGID. These issues include:

- Access to health care and the socio-economic and socio-cultural factors that determine it.
- Societal and health care providers' attitudes to FGIDs (focusing on governmental and private insurance).
- The percentage of the population covered by the different systems/providers (e.g., national health or social security, private insurance, partial subsidy, patient co-payment/private practice) in the countries assessed.
- The level at which FGID patients are treated (e.g., primary care, tertiary care hospitals).
- Which diagnostic procedures are used to diagnose FGIDs and to what extent?
- Knowledge and use of the Rome diagnostic criteria by physicians.
- Availability of medications for FGIDs and the process of registration and approval of new drugs.
- Expenditures on healthcare for FGIDs, both by the government and by patients out-of-pocket.

- Use of complementary and alternative medicine (CAM) for FGIDs.

To fulfil this task, we compared a European country, Italy, which has universal health care coverage with India, Mexico and South Korea. Both India and Mexico are developing countries or newly industrialized ones. India is considered a leading emerging economy included in the so-called BRICS: Brazil, Russia, India, China and South Africa (78), while Mexico and South Korea are emerging fast-track markets belonging to the so called MISTs: Mexico, Indonesia, South Korea, and Turkey (79). The MISTs emerging markets are the four biggest ones in the Goldman Sachs N-11 Equity Fund, and their economies more than doubled in size in the past decade, topping Germany last year (80).

***The population sectors covered by healthcare systems/providers.***

***Italy***

In Italy, there is a national healthcare service for all residents, irrespective of gender, age, education, and socioeconomic status. There is universal and free coverage for consultations and diagnostic investigations for low-income people, which are otherwise also available with co-payment. There are also private practice and private insurance systems. Italian citizens, who are beneficiaries of the National Health System (NHS), can use private practice as an alternative or in addition to the NHS.

***India***

National healthcare services are available for all residents irrespective of age, gender, education, and socioeconomic status. According to the Indian constitution the state government is responsible for providing healthcare services to its people. However, due to insufficient resources, manpower and infrastructure, the government is unable to provide for the entire population. Hence, people have to use other healthcare service providers such as private hospitals, dispensaries, nursing homes (small private hospitals), non-government organization and international agencies. The quality and availability of these services vary between urban and rural areas, and from state to state.

According to the National Family Health Survey, the private medical sector is the primary source of health care for the majority of households in both urban (70%) and rural areas (63%) of India (81). There is open access and patients can choose where to consult

(private and government; primary, secondary or tertiary level) and can even transfer freely from one system to another without restriction, irrespective of whether they have private insurance coverage or whether they have consulted previously at a government healthcare center. The government's primary healthcare system in India is organized in three levels of care (Subsidiary Health Center, Primary Health Center, and Community Health Center) based on population norms. The secondary and tertiary care government institutions include district hospitals, Medical College Hospitals, and Superspeciality Teaching Institutions. Over 72% of the population in India lives in rural areas and the above-mentioned system provides healthcare to this population. Other modalities such as alternative medicine (e.g., allopathic, homeopathic, Ayurvedic, Unani, Siddi, etc.) are available and private practitioners, non-government organizations such as the Red Cross, international agencies like CARE (Co-operative for Assistant and Relief Everywhere), also provide health services in the rural areas (81).

### **Mexico**

In theory, 97% of the population currently has health coverage although the quality of care may differ by provider system. In the Mexican model of healthcare the population is divided into two groups, the "insured ones" who are insured through a Social Security System and the "uninsured ones." The Social Security Systems are responsible for providing healthcare to public workers (public institutions and government) and private workers. The uninsured are made up of people at the two ends of the economic spectrum, i.e., the middle and high socioeconomic class who avail themselves of private healthcare with out-of-pocket resources or private insurance coverage, and the very poor who are supposed to be covered by the Popular Insurance, created by the government (82). With this background, it is generally held that 43% of the population is covered by the Mexican Institute of Social Security, 9% by the Institute of Social Security of State Workers, and 1% by other Social Security Systems, such as the Mexican Petroleum Company, and the Army and Marine Forces. One percent of the population has private insurance and 2% use other providers. The recently created government Popular Insurance supposedly covers 40% of the population (84, 85).

### **South Korea**

In Korea, the National Health Care Insurance System (NHI) has been widening its coverage since 1977 when the government launched it (83). The coverage has increased from 8.8% of the population in 1977 to almost 97% in 2011 (1977: 8.8%, 1989: 90.4%, 2000: 96.7%, 2011: 96.8%) (84). Therefore, most Koreans are covered under this system.

### **Where in the healthcare system are FGID patients treated?**

#### **Italy**

There is national healthcare coverage for diagnostic tests and procedures for all residents of Italy and citizens of the European Union. Ninety percent of patients with FGIDs are followed by general practitioners (GPs) and about 5% are referred to gastroenterologists. A study among GPs from the province of Pisa, representing 10% of the total list of GPs for the Public Health Service of the region, showed that the number of patients who consulted for IBS was  $6.6 \pm 4.3$  per month per 1,000 patients (median: 5.3, range: 0.8-14.7) and 26.2% were newly diagnosed IBS patients (85). Of the IBS cases, 63.3% were referred to at least one specialist (37.6% gastroenterologists, 19.9% psychologists/psychiatrists, 12.1% dieticians, and 18.6% of the women to gynecologists). The most common reasons for referrals were the need for further diagnostic testing in 28.4% of the cases, need for reassurance in 12.9%, patient's request in 12%, therapeutic failure in 11.6%, difficult patient to manage in 10.7%, and others in 3.6%.

#### **India**

There is open access to healthcare, so patients choose where they consult, and can transfer from one service to another without restriction. Some FGID patients can turn directly to a tertiary care facility for consultation. There is no formal referral system.

#### **Mexico**

In Mexico there is little information on the level of care at which patients with FGIDs/IBS consult. In the Mexican Institute of Social Security the majority of the patients with IBS are cared for in family medicine units. In fact, a study that evaluated the prevalence of IBS among patients between 20 and 49 years of age who consulted at a family medicine unit in the state of Guanajuato, determined that 35%

of the patients had IBS according to the Rome II criteria (86).

Family physicians take care of IBS patients in the family medicine units of the IMSS. Patients have to come to them to get a referral to the second level of care. In the Institute of Social Security of State Workers, 50% of the consultations at gastroenterology clinics are for IBS (87). In private practice, patients with IBS consult with specialists in many medical disciplines including surgeons, gynecologists, gastroenterologists and internists (88).

### ***South Korea***

Most patients with IBS (98.6%) consult at outpatient clinics and 1.9% are treated there. According to the healthcare institutions, the proportion of IBS patients consulting at primary care clinics is 78.3% and the proportion using referral centers (general hospitals and teaching hospitals) is 15.2%. The National Evidence-based Healthcare Collaboration Agency has estimated the number of outpatient visits per year for IBS patients at  $2.5 \pm 4.0$  (mean  $\pm$  SD) and the days of hospital stay in case of inpatients at  $14.7 \pm 25.0$  days. Frequent medical service users ( $\geq 3$  consultations per year), consulted the same hospital in 78.5% of the cases, while 18.5% consulted at two different healthcare centers, 2.9% consulted at three centers, and 0.3% at four centers (89).

### ***Which diagnostic procedures are used for FGIDs and to what extent?***

#### ***Italy***

After a clinical evaluation, GPs ordered diagnostic tests in 86.3% of patients with IBS. The most common tests were complete blood count in 74.7% of the cases, thyroid function tests in 36.0%, lower endoscopies in 31.1%, barium enema in 21.8%, upper endoscopies in 12.0%, fecal occult blood test in 38.7%, stool analysis (ova and parasites and culture for bacterial pathogens) in 36.9%, lactose breath test in 5.8%, and abdominal ultrasound in 41.3% (85). However, the cost of upper gastrointestinal endoscopy is very low and can explain why 61.6% of dyspeptic patients with predominant epigastric pain and 35.0% of those with non-painful symptoms visiting GPs, are referred for endoscopy independent of age (90).

#### ***India***

Many of the diagnostic procedures are available through open access, including upper gastrointestinal endoscopies, colonoscopies

and ultrasound. The treating physician decides on the indication and the waiting time is quite short if patients agree to undergo the procedure, particularly in the private sector. In a study based on 2,549 presumably healthy adults in an urban area (Mumbai), 1,695 (66.5%) had neither dyspepsia nor IBS, 774 (30.4%) had dyspepsia, 6.5% both dyspepsia and IBS, and 4.7% IBS alone. The reported frequency of consultations was 24.1% among those with dyspepsia alone, 40.9% among those with both dyspepsia and IBS and 10% among those with IBS alone, while only 0.1% reported not having any functional GI symptoms (91). Patients with both dyspepsia and IBS underwent gastroscopy (10%) more often than those with dyspepsia alone or IBS alone (3.6 vs. 1.3%, respectively). The same was also observed for abdominal ultrasounds: (15.5% vs. 5.9% vs. 1.3%). This is the only study that has analyzed the use of diagnostic testing in subjects with FGIDs in India (91). It is important to note that the cost of an upper gastrointestinal endoscopy may be in the range of \$10 and \$25 USD.

#### ***South Korea***

It has been reported that 55.7% of IBS patients in South Korea underwent colonoscopy, 27.5% abdominal ultrasound, and 14.3% abdominal CT scan. Other investigations that are carried out in IBS patients include urine analysis in 36.3%, sigmoidoscopy in 7.3%, barium enema in 7.3%, upper endoscopy in 53.8%, abdominal MRI in 1.5%, PET-CT in 0.7%, and a routine screening survey in 5.5%. In addition, they underwent some of the procedures more than once. For example, colonoscopies 1.5 times on average, sigmoidoscopies 1.2 times and abdominal ultrasound 1.6 times (89).

#### ***Mexico***

In 1998, a retrospective study of IBS-Rome I patients who consulted at a tertiary referral academic center in Mexico City showed that over a follow-up period of 33.4 months (range: 1-243), a median of 22.4 (range: 1-82) studies were ordered per patient. Of these, five (range: 1-11) were done before IBS was diagnosed and 17.4 (range: 1-18) afterwards, even though in 87% of the cases, the diagnosis was established during the first visit based on clinical criteria (92). It was interesting that some of the tests such as blood chemistry were ordered up to 18 times, and blood cell counts up to 10 times. Only 50% of the patients had a stool examination for ova and parasites and

24% did not undergo any study to visualize the colon (i.e., barium enema, colonoscopy, flexible sigmoidoscopy). Each patient consulted on average 3.6 times a year. The reasons for consultations were gastrointestinal symptoms in 44.2% and non-gastrointestinal symptoms in 48.6%.

### ***Knowledge and use of the Rome diagnostic criteria***

#### ***Italy***

Italian GPs do not routinely use the Rome criteria, although many of them know of their existence. In the study among GPs from the province of Pisa, only 35.7% of those surveyed (N=28) stated that they were familiar with the Rome II criteria and six of them (21.4%) used them in their practice. Furthermore, 60.7% judged their personal knowledge of IBS to be insufficient, but only three (10.7%) felt that further educational training would be useful (85). However, they correctly detected changes in bowel habit followed by abdominal pain, discomfort and bloating, as the most important symptoms to diagnose IBS. Furthermore, about 20% of the patients were diagnosed as IBS even though they did not report abdominal pain or discomfort.

#### ***India***

The Rome criteria are not commonly accepted in India. GPs are not familiar with them and even among many gastroenterologists who care for patients with IBS, it is commonly believed that the Rome criteria may not be very applicable in India as pain and discomfort, which are essential to the diagnosis of IBS using the Rome criteria, are not reported by 30% of patients diagnosed with IBS.

However, a combination of abdominal pain or discomfort or lower abdominal fullness relieved by defecation, was reported by 90% of patients complaining of lower gastrointestinal symptoms with no alarm features and negative investigations for organic disorders, suggesting a lower abdominal FGID (93). Also, Manning and Rome I criteria seem to detect more IBS patients than Rome II or III (8, 93, 94). The Asian Criteria include recurrent abdominal pain, bloating, or any other discomfort for  $\geq 3$  months, associated with one or more of the following: (a) relief with defecation, (b) change in stool form (identified by patients using the Bristol Stool Scale), and (c) change in stool frequency (95). The most common

reason for not fulfilling Rome criteria were the absence of “more frequent stools with onset of pain,” “loose stool with onset of pain,” “relief of pain with passage of stool,” “bloating,” and a minority did not meet the duration of symptoms criterion. Moreover, because of the fact that 56% of people from India pass one or two bowel movements per day, Rome I or II criteria may not be adequate for subclassifying IBS into constipation or diarrhea.

#### ***Mexico***

The data confirm that physicians in Latin America accept the Rome criteria for IBS, mainly the Rome III criteria, but a third of them don't really know these criteria, especially physicians working in private practice.

The majority reported using the Rome III criteria and when asked to identify the different criteria, as presented in a series of questions with multiple choices, the correct identification of the Rome III by those reporting that they used them in clinical practice vs. those who did not, was 72% vs. 33.3% ( $p < 0.05$ ) (96).

### ***Available/approved medications for FGIDs***

In contrast to the US, a wide variety of prokinetic agents and anti-spasmodic agents are available in these countries. Rifaximin is also approved in all four countries. In contrast, indications for psychotropic agents are restrictive.

#### ***Italy***

In the GPs study from Pisa, antispasmodics (40%) were the most commonly prescribed medications for IBS followed by probiotics (30%) and anxiolytics (20%). Patients with diarrhea-predominant IBS (IBS-D) were given prescriptions more commonly than those with constipation-predominant IBS (IBS-C) (91.4 vs. 55.7%,  $p = 0.001$ ) (85).

#### ***India***

In India it was reported that 34% of patients with IBS in a tertiary care center (the All India Institute of Medical Science) were treated with anti-depressant drugs (97). On the other hand, in a study in a tertiary care center in which 79.9% of the IBS patients compared to 34.3% of the controls had psychiatric co-morbidities, only 7.6% of the IBS patients were receiving specific medication for these co-morbidities (98).

### **Mexico**

Antispasmodics are the most commonly used medications for IBS in Mexico. Anti-depressants are approved for IBS. In addition, Tegaserod is still available in Mexico.

### **South Korea**

Antidepressants are not approved for IBS in South Korea so patients have to have a psychiatric disorder in addition to IBS for physicians to prescribe these agents for them,

### **Expenditures on FGID health care, by the government and by patients out-of-pocket.**

#### **Italy**

None of the drugs used for FGIDs is covered by the healthcare system. A recent national Italian survey on functional constipation (FC) indicated that the mean annual indirect cost for patients with FGIDs is \$5,100 US dollars (99). The mean cost for diagnosing IBS was reported to be \$85.7 US dollars.

Drugs for other conditions than FGIDs, e.g., anti-depressants, can be used for FGIDs and are covered by the NHS.

#### **India**

The government system of healthcare in India either covers patients' expenses in their entirety or is highly subsidized, varying from 25% to 100% of the coverage. Only a minority of people has insurance coverage. There is no information about expenditures related to FGIDs. However, in terms of the costs of medications most of the available ones are either generic or are specially priced for the Indian market. Hence, the cost of most drugs is quite low.

### **Mexico**

As part of a nationwide clinical study in Mexico, the average monthly expense per IBS patient, independent of IBS subtype, was estimated to be \$107 USD. Expenses included endoscopy and imaging studies \$224±25, prescription medications \$152±11, medical consultations \$138±10, laboratory tests \$106±10, and transportation costs \$22±3. Furthermore, if patients consulted more than three times per month (6% of the cases), the expenses increased to \$200-700 USD. It is noteworthy that 52% of the patients in this study earned less than \$500 US dollars per month and the minimum wage at the time of the study (2011) was approximately \$150 dollars per month (100).

### **South Korea**

The total reimbursement for IBS incurred during 2008 (NHI costs) was estimated at \$154 million USD, which corresponds to approximately 0.46% of the total reimbursements for the entire population of South Korea at 33.4 billion dollars (83). The average annual NHI cost per IBS patient was \$64.1 USD (SD - \$237.2 USD, Median - \$19.1 USD); the cost per outpatient was \$43.7 USD and per admission \$1087.9 USD. The mean NHI cost per women was lower than that for men (\$60.8 USD vs. \$68.6 USD), however, the total cost for women with IBS was higher than for men because of female predominance in this disorder. Medical costs were highest for middle aged (40-59 years), followed by older adults (≥ 60 years) and young adults (30 to 39 years). The mean NHI cost per IBS patient was higher in teaching hospitals (\$181.6 USD), and lower in primary care clinics (\$36.1 USD). However, the total amount of NHI costs for IBS was \$68.2 USD in primary clinics, \$44.9 USD in general hospitals, and \$14.0 USD in teaching hospitals (83).

### **Use of CAM for FGIDs**

#### **Italy**

CAM was used by 48.7% and diet and/or dietary supplementation by 64.3% of the patients. These treatments were used in the majority of cases in addition to conventional therapy. Among CAM, the most frequent types were herbal products (36.7%), homeopathy (17.1%), relaxation (5.5%), and acupuncture (3.5%). Dietary approaches consisted mostly of empirical exclusion diets (39.7%), probiotics (31.7%) or prebiotics and/or fiber supplements (22.6%). The use of CAM was motivated by the belief that it is natural (39.9%), harmless and safer than conventional drugs (34.3%), makes one feel better (14.7%), and acts more gently and holistically (11.2%) (101).

#### **India**

A large number of alternative treatments including ancient traditional medicine systems such as homoeopathy and Ayurveda are available in India. However, no information is available on the prevalence of CAM usage by patients with IBS.

### **Mexico**

One study reported that the use of CAM was more frequent among IBS patients than FD or GERD patients (51% vs. 36 vs. 27%) (102). Predictors of CAM use were past

abdominal surgeries, IBS, more than three consultations during the previous year, visits to the emergency room, sick leave because of FGIDs, and a history of taking benzodiazepines. Types of CAM included herbal medicines (86%), nutritional therapies (44%), homeopathic remedies (15%), acupuncture (9%) and others (5%) including reflexology, witchcraft, magnet therapy, aromatherapy, consumption of human colostrum, and bull's gall. CAM was recommended by relatives in 55% of the cases, friends in 33% and physicians in 4%, while 8% learned about CAM from the media and other sources.

### ***South Korea***

In South Korea IBS patients reported using alternative therapeutic options such as over-the-counter medications (8.1%), functional health foods (8.4%), health aid tools (4.8%), and folk remedies (8.8%) (102).

***Appendix 6. Cross-cultural multinational research: intra-family illness behavior dynamics***

***Rona L. Levy, Shin Fukudo, Charles Gerson, Ami Sperber, Mary-Joan Gerson***

An important potential area of interest in IBS research is the cross-cultural analysis and comparison of intra-family illness behavior dynamics. The way families interact in response to illness, and other intra-familial relationships (both healthy and dysfunctional) can have an important impact on the clinical pattern of many diseases (103). Family constellations and dynamics (rules, responsibilities, expectations, alliances) are different around the world, and also are changing rapidly because of globalization and traumatic conflicts leading, among other results, to increased internal migration. Cross-cultural, multinational research into intra-family illness dynamics in both the pediatric and adult age groups can provide important information on similarities and differences in these patterns, which could be used for understanding, prevention and treatment across cultures.

Specifically, increased insight into the ways in which IBS and family relationships affect each other could improve patient care. Based on this knowledge physicians and other health care providers can help patients and their families develop coping skills to improve their relationship quality with a beneficial effect on the IBS patient. Health professionals can be encouraged to inquire about family relationships in culturally appropriate ways, which would improve the connection with the patient, thus opening up a discourse that could lead to greater patient insight about the context of their illness.

The subject of intra-family illness behavior dynamics has been investigated in some areas of the world (for example, the USA and Japan), but the cross-cultural perspective has received little attention. One valuable review of the literature on this subject was recently published (104). Reports limited to single populations have found that partners of IBS patients bear a significant burden compared to partners of healthy individuals (105). Moreover, children of mothers with IBS have more illness behavior, both gastrointestinal and otherwise, than children of controls (106). IBS patients have a poorer social support network than controls (107).

Among the cross-cultural issues studied in IBS are specific cultural premises affecting family functioning and structure, such as:

- The effects of culture and politics on family life.
- Internal migration resulting in urban versus rural contexts; gender roles and expectations.
- Conflict vs. support from an IBS patient's family members.

The results of an 8-country cross-cultural study showed that family conflict is associated with greater IBS symptom severity, while family support and depth of relationship is associated with lesser symptom severity (12).

When comparing different cultures and geographical areas, most IBS research has utilized familiar IBS measures such as symptom severity, Rome criteria, and quality of life. The use of cross-cultural and family investigational tools will enrich these results by first testing their psychometric properties across cultures. Collaboration with scientists from the fields of family psychology and medical anthropology, who are familiar with the use of appropriate, relevant and reliable questionnaires, is encouraged. Thus, identifying potential collaborators is a key step in at the study planning and design of the research.

As one goal of the research is to examine family factors and cultural beliefs, use of interview techniques will add depth to the findings. Some researchers have used teams of local health workers to ensure that a community study conforms to rigorous standards of data collection. This can also help when translation is an issue.

The following three abstracts provide examples of ideas for potential cross-cultural research relating to intra-family illness behavior dynamics. They are presented as abstracts that highlight not only the background and methods, but also the innovativeness and potential significance of each study. The purpose here is to demonstrate how cross-cultural research into intra-family illness behavior dynamics can be conceived, designed and operationalized into a cross-cultural, multinational research project.

***A comparative study of the effect of IBS on HRQOL in patients and their life partners in different geographic regions and cultural groups***

***Ami Sperber***

**Background/Significance:** Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that has a deleterious effect on patients' health-related quality of life (HRQOL). Very little is known on its effect on HRQOL in different cultural groups and geographical areas, nor is there information of the effect of this chronic disorder on the quality of life of IBS patients' life partners. The results of the study can provide new insights into how patients and their significant partners perceive illness and HRQOL in various cultural groups and to further our ability to foster a therapeutic partnership with our patients and their life partners that is relevant to the needs of patients and their life partners in different cultures.

**Innovation:** Although it is reasonable to assume that the quality of life of the patients' life partners may be adversely affected, this aspect has never been evaluated to our knowledge in a multinational, cross-cultural study. This is of particular interest as the style of involvement in health care by life partners and other family members varies from region to region and culture to culture. The proposal is to conduct a cross-cultural study to assess HRQOL among IBS patients and their life partners compared with healthy controls and their life partners.

**Methods:** A cross-cultural observational study to assess HRQOL among IBS patients and their life partners compared with healthy controls and their life partners (matched by age and gender), using validated HRQOL, coping skills, and psychological questionnaires.

The primary study aim will be to compare the HRQOL of life partners of IBS patients to the life partners of healthy controls in different cultural groups and geographical regions. The study population size will be calculated to provide statistical power to achieve this study aim. The secondary aims will be to assess differences in perception of HRQOL between patient and life partners, to assess associations between coping skills and HRQOL between IBS patients and their life partners compared with healthy controls and their life partners in each country or cultural group.

**Investigator(s).** Leading IBS researchers in different countries/cultural groups will be invited to participate. An alternative method is to recruit study investigators by open invitation, so that as many countries/cultural groups as would be interested in doing so could participate in the study.



***Cross-cultural study of family beliefs regarding IBS symptom attribution.***

***Mary-Joan Gerson and Charles D. Gerson***

**Background:** Local cultural beliefs can affect the way people process physical symptoms. Symptoms can be attributed to various sources, mainly divided into physical causes such as infection, inflammation, allergy, maldigestion and to psychological causes such as emotional distress, imbalance with the environment, and interpersonal tensions. Beliefs about IBS are culturally variable, partly as a result of the mystery that surrounds functional gastrointestinal disorders.

Family or other intimate relationships have been reported to affect the illness experience of patients with IBS and other chronic illnesses. Family members may have beliefs about IBS that are different from the patient. This study will investigate beliefs addressing the question: What is seen as the cause of IBS symptoms? It is possible that similar beliefs among family members or married couples can facilitate coping and lower symptomatology. On the other hand, it may not be general differences that matter but specific discrepancies such as the partner emphasizing psychological causality and the patient physiological causality. This will be the first study examining belief systems about IBS causality within family structures.

**Methods:** The IBS Mind-Body Belief Scale is divided into ten “physical” and ten “psychological” attributions regarding the cause of IBS. This scale has been validated with a high Cronbach reliability score and has been used in several research studies. In one international study involving eight countries, a stronger belief in physical causation correlated with higher IBS symptom severity, while a stronger belief in psychological causation correlated with lower symptom severity. In addition, there were significant differences among geographic sites, with China scoring highest on “mind” agreement and China and India scoring highest on “body” agreement.

IBS patients will complete the IBS symptom severity scale. They and family members (close relationships) will complete the IBS Mind-Body Belief Scale.

**Results:** Compare Mind-Body scores for each location, between intimately related individuals and IBS patients.

Compare correlations between the IBS SSS and the Mind-Body Scale for each location, between patients and relation

### ***Intergenerational transmission of illness behavior***

**Rona L. Levy**

**Significance:** Functional abdominal pain in childhood has been shown to be a precursor to functional GI problems in adulthood. A significant body of literature exists in the United States that links specific parental cognitions and behaviors with the development and maintenance of abdominal pain in children. This has led to some clinical recommendations and suggestions for further research into more fine-grained analyses of these variables. If successful, this work has the potential for preventing a lifetime of disability in many individuals. However, attempts to replicate these findings in a different culture (specifically Japan) have led to contrary findings, despite the fact that questionnaires utilized in US studies were translated following strict translation protocols. The possibility exists that the translation of cultural constructs, rather than merely words and phrases, may be more complex (for example, what is reinforcing in one culture may not be in another). In other words, the translation should be culturally adapted rather than literal. An alternative explanation to the contrary findings is that there are true differences in intergenerational transmission among different cultural groups, unrelated to translation issues. To explore the mechanisms by which the intergenerational transmission of illness behavior explored in the US operates cross-culturally, the development and testing of culture-specific instruments is necessary.

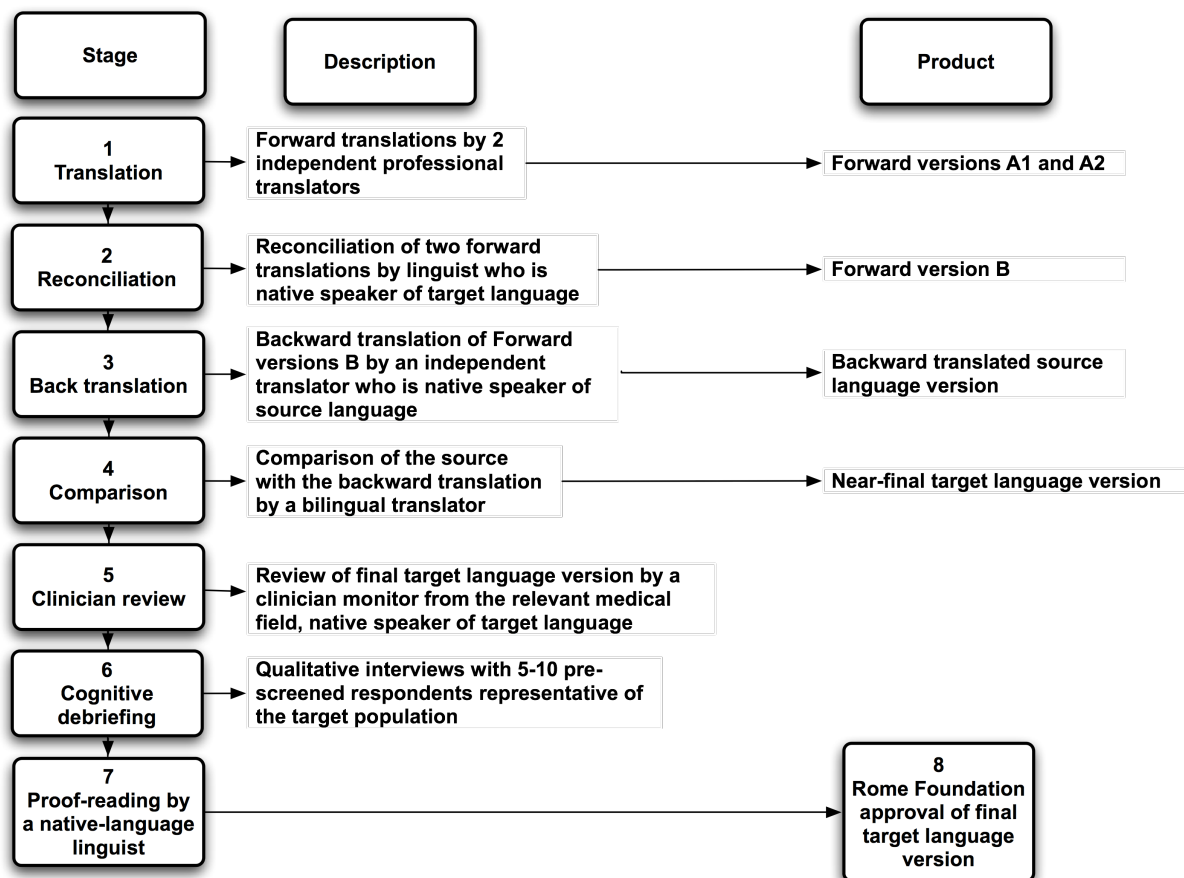
**Innovation:** There has been no coordinated research exploring this particular phenomenon of intergenerational transmission across several cultures.

**Methods:** The initial phase of the research would involve the development of several questionnaires utilized in US studies in at least five separate cultures around the globe. After development, in a second phase questionnaires would be administered to at least 200 parent-child pairs in each of these cultures. Ultimately, in a third phase, treatment protocols developed from these findings would be tested in these same cultures.

**Investigator(s).** All researchers would be selected based on their expertise, and all researchers would work as a team, sharing information through regular and frequent communications.

**Environment:** Environments are at present undetermined, and are dependent on researcher selection. Nevertheless, it is expected academic institutions would have some involvement in each site.

**Fig. 1. Rome Foundation translation and cultural adaptation process.**



## Bibliography

1. Sperber AD. The challenge of cross-cultural, multi-national research: potential benefits in the functional gastrointestinal disorders. *Neurogastroenterol Motil.* 2009;21:351-60.
2. Sperber AD, Drossman DA, Quigley E. IBS – The global perspective (a Rome Foundation-WGO symposium). *Am J Gastroenterol.* 2012;107:1602-9.
3. Quigley EM, Abdel-Hamid H, Barbara G, Bhatia SJ, Boeckxstaens G, De Giorgio R, et al. A global perspective on irritable bowel syndrome: a consensus statement of the World Gastroenterology Organisation Summit Task Force on irritable bowel syndrome. *J Clin Gastroenterol.* 2012;46:356-66.
4. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther.* 2003;17:643-50.
5. Zuckerman MJ, Guerra LG, Drossman DA, Foland JA, Gregory GG. Comparison of bowel patterns in Hispanics and no-Hispanic whites. *Dig Dis Sci.* 1995;40:1763-9.
6. Sperber AD, Friger M, Shvartzman P, Abu-Rabia M, Abu-Rabia R, Abu Rashed M, et al. Rates of functional bowel disorders among Israeli Bedouins in rural areas compared to those who moved to permanent towns. *Clinical Gastroenterology and Hepatology.* 2005;3:342-8.
7. Seifert B, Rubin G, de Wit N, Lionis C, Hall N, Hungin P, et al. The management of common gastrointestinal disorders in general practice A survey by the European Society for Primary Care Gastroenterology (ESPCG) in six European countries. *Dig Liver Dis.* 2008;40(8):659-66.
8. Gwee KA, Bak YT, Ghoshal UC, Gonlachanvit S, Lee OY, Fock KM, et al. Asian consensus on irritable bowel syndrome. *J Gastroenterol Hepatol.* 2010;25:1189-205.
9. Kanazawa M, Whitehead WE, Palsson OS, Turner MJ, Shinozaki M, et al. Medical care for irritable bowel syndrome (IBS) in Japan compared to the US. *Digestive Disease Week 2012; May 7-10, 2012; Chicago, Illinois 2012.*
10. Kellow J, Lee OY, Chang FY, Thongsawat S, Mazlam MZ, Yuen H, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. *Gut.* 2003;52:671-6.
11. Muller-Lissner S, Rykx A, Kerstens R, Vandeplasse L. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. *Neurogastroenterol Motil.* 2010;22:991-8.
12. Gerson MJ, Gerson CD, Awad RA, Dancey C, Poitras P, Porcelli P, et al. An international study of irritable bowel syndrome: family relationships and mind-body attributions. *Soc Sci Med.* 2006;62:2838-47.
13. Kanazawa M, Drossman DA, Shinozaki M, Sagami Y, Endo Y, Palsson OS, et al. Translation and validation of a Japanese version of the irritable bowel syndrome-quality of life measure (IBS-QOL-J). *Biopsychosoc Med.* 2007;1:6.
14. Shinozaki M, Kanazawa M, Palsson OS, Sagami Y, Endo Y, Hongo M, et al. Validation of the Japanese version of comorbid conditions questionnaire (CCQ-J) and recent physical symptoms questionnaire (RPSQ-J). *Intern Med.* 2011;50:375-80.
15. Thompson WG, Drossman DA, Talley NJ, Walker L, Whitehead WE. Rome III diagnostic questionnaire for the adult functional GI disorders (including alarm questions) and scoring algorithm. In: Drossman DA, Cprazzoaro E, Delvaux M, Spiller RC, Talley NJ, Thompson WG, et al., editors. *Rome III: The Functional Gastrointestinal Disorders. III.* McLean, VA: Degnon Associates, Inc.; 2006. p. 917-51.
16. Kulis D, Arnott M, Greimel ER, Bottomley A, Koller M. Trends in translation requests and arising issues regarding cultural adaptation. *Expert Rev Pharmacoecon Outcomes Res.* 2011;11:307-14.
17. Sperber AD, DeVellis RF, Boehlecke B. Cross-cultural translation: methodology and validation. *Journal of Cross-Cultural Psychology.* 1994;25:501-24.

18. Diaz-Loving R. Contributions of Mexican ethnopsychology to the resolution of the etic-emic dilemma in personality. *Journal of Cross-Cultural Psychology*. 1998;29:104-18.
19. Brislin R, Lonner W, Thorndike R. Questionnaire wording and translation. *Cross-cultural research methods*. New York: Wiley; 1973. p. 32-58.
20. Brislin RW. Translation and content analysis of oral and written material. In: Triandis HC, Berry JW, editors. *Handbook of Cross-Cultural Psychology*. 2. Boston: Allyn and Bacon; 1980. p. Chapter 10.
21. Prince R, Mamboour W. A technique for improving linguistic equivalence in cross-cultural surveys. *Int J Soc Psychiatry*. 1967;13:229-37.
22. FDA & US Department of Health and Human Services. Guidance for Industry. Patient-reported outcome measures: use in medical product development to support labelling claims 2009. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.
23. Dewolf L, Koller M, Velikova G, Johnson C, Scott N, Bottomley A, et al. EORTC Quality of Life Group Translation Procedure. In: Group EQoL, editor. 3rd ed. Brussels, Belgium: EORTC; 2009.
24. Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. *Value in Health*. 2009;12:419-29.
25. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health*. 2005;8:94-104.
26. Gwaltney C, Shields A, Shiffman S. White Paper PRO Consulting: Equivalence of Computerized and Paper and Pencil PRO Measures. In: Consulting P, editor. Pittsburgh, PA2006.
27. Gerson CD, Gerson MJ. Technical report: an ePRO patient reported outcome program for the evaluation of patients with irritable bowel syndrome. *NeurogastroenterolMotil*. 2013;(in press).
28. Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. *Value Health*. 2008;11:322-33.
29. Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington, VT: University of Vermont Department of Psychiatry; 1991.
30. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Appendix C. Rome III Diagnostic Questionnaire for the Adult Functional GI Disorders (including Alarm Questions) and Scoring Algorithm. In: Drossman SA, Corazziari E, Delvaux M, Spiller RC, Talley NJ, Thompson WG, et al., editors. *Rome III The Functional Gastrointestinal Disorders*. McLean, Virginia: Degnon Associates, Inc.; 2006. p. 487-555.
31. Talley NJ, Phillips SF, Wiltgen CM, Zinsmeister AR, Melton LD. Assessment of functional gastrointestinal disease: the bowel disease questionnaire. *Mayo Clin Proc*. 1990;65:1456-79.
32. Sperber AD, Carmel S, Atzmon Y, Weisberg I, Shalit Y, Neumann L, et al. Use of the Functional Bowel Disorder Severity Index (FBDSI) in a study of patients with the irritable bowel syndrome and fibromyalgia. *Am J Gastroenterol*. 2000;95:995-8.
33. Drossman DA, Li Z, Toner BB, Diamant NE, Creed FH, Thompson D, et al. Functional Bowel Disorders. A multicenter comparison of health status and development of illness severity index. *Dig Dis Sci*. 1995;40:986-95.
34. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*. 1997;11:395-402.
35. Bharucha AE, Locke GR, 3rd, Seide BM, Zinsmeister AR. A new questionnaire for constipation and faecal incontinence. *Aliment Pharmacol Ther*. 2004;20:355-64.

36. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantoni C, Thorson AG, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. *Dis Colon Rectum*. 1999;42:1525-32.
37. Frank L, Kleinman L, Farup C, Taylor L, Miner P, Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol*. 1999;34:870-7.
38. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473-83.
39. de Bruin AF, Diederiks JP, de Witte LP, Stevens FC, Philipsen H. The development of a short generic version of the Sickness Impact Profile. *J Clin Epidemiol*. 1994;47:407-18.
40. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy*. 1990;16:199-208.
41. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci*. 1998;43:400-11.
42. Hahn BA, Kirchdoerfer LJ, Fullerton S, Mayer E. Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome. *Aliment Pharmacol Ther*. 1997;11:547-52.
43. Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. *Scand J Gastroenterol*. 2005;40:540-51.
44. el-Omar EM, Banerjee S, Wirz A, McColl KE. The Glasgow Dyspepsia Severity Score--a tool for the global measurement of dyspepsia. *Eur J Gastroenterol Hepatol*. 1996;8:967-71.
45. Rabeneck L, Cook KF, Wristers K, Soucek J, Menke T, Wray NP. SODA (severity of dyspepsia assessment): a new effective outcome measure for dyspepsia-related health. *J Clin Epidemiol*. 2001;54:755-65.
46. Fraser A, Delaney BC, Ford AC, Qume M, Moayyedi P. The Short-Form Leeds Dyspepsia Questionnaire validation study. *Aliment Pharmacol Ther*. 2007;25:477-86.
47. Goldman J, Conrad DF, Ley C, Halperin D, de la Luz Sanchez M, Villacorta R, et al. Validation of Spanish language dyspepsia questionnaire. *Dig Dis Sci*. 2002;47:624-40.
48. Rentz AM, Kahrilas P, Stanghellini V, Tack J, Talley NJ, de la Loge C, et al. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. *Qual Life Res*. 2004;13:1737-49.
49. De La Loge C, Trudeau E, Marquis P, Revicki DA, Rentz AM, Stanghellini V, et al. Responsiveness and interpretation of a quality of life questionnaire specific to upper gastrointestinal disorders. *Clin Gastroenterol Hepatol*. 2004;2:778-86.
50. Talley NJ, Verlinden M, Jones M. Validity of a new quality of life scale for functional dyspepsia: a United States multicenter trial of the Nepean Dyspepsia Index. *Am J Gastroenterol*. 1999;94:2390-7.
51. Chassany O, Marquis P, Scherrer B, Read NW, Finger T, Bergmann JF, et al. Validation of a specific quality of life questionnaire for functional digestive disorders. *Gut*. 1999;44:527-33.
52. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, et al. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. *Qual Life Res*. 2004;13:833-44.
53. Svedlund J, Sjodin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci*. 1988;33:129-34.
54. Shaw M, Talley NJ, Beebe T, Rockwood T, Carlsson R, Adlis S, et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. *Am J Gastroenterol*. 2001;96:52-7.

55. Eypasch E, Williams JJ, Wood-Dauphinée S, Ure B, Schmülling C, Neugebauer E, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg*. 1995;82:216-22.
56. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361-70.
57. Palsson OS, Jones KR, Turner MJ, Drossman DA, Whitehead WE. Development of specific questionnaires to assess somatization and comorbid diagnosis in irritable bowel syndrome (IBS). *Gastroenterology*. 2002;122 (suppl 1):A502.
58. Rosenstiel AK, Keefe FJ. The use of cognitive coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. *Pain*. 1983;33-44.
59. Labus JS, Bolus R, Chang L, Wiklund I, Naesdal J, Mayer EA, et al. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment Pharmacol Ther*. 2004;20:89-97.
60. Shaw M, Talley NJ, Adlis S, Beebe T, Tomshine P, Healey M. Development of a digestive health status instrument: tests of scaling assumptions, structure and reliability in a primary care population. *Aliment Pharmacol Ther*. 1998;12:1067-78.
61. Toner BB, Stuckless N, Ali A, Downie F, Emmott S, Akman D. The development of a cognitive scale for functional bowel disorders. *Psychosom Med*. 1998;60:492-7.
62. Antonovsky A. *Unraveling the Mystery of Health*. San Francisco, CA: Jossey-Bass; 1987.
63. Antonovsky A. The structure and properties of the Sense of Coherence scale. *Soc Sci Med*. 1993;36:725-33.
64. Whorwell PJ. Unraveling functional abdominal bloating and distension: the role of thoraco-abdominal accommodation and a physical sign to aid its detection. *Neurogastroenterol Motil*. 2012;24:301-4.
65. Gerson CD, Gerson MJ, Awad RA, Chowdhury A, Dancy C, Poitras P, et al. Irritable bowel syndrome: an international study of symptoms in eight countries. *Eur J Gastroenterol Hepatol*. 2008;20:659-67.
66. Grunert SC, Scherhorn G. Consumer values in West Germany underlying dimensions and cross-cultural comparison with North America. *Journal of Business Research*. 1990;20:97-107.
67. Koller M, Kantzer V, Mear I, Zarzar K, Martin M, Greimel E, et al. The process of reconciliation: evaluation of guidelines for translating quality-of-life questionnaires. *Expert Rev Pharmacoecon Outcomes Res*. 2012;12:189-97.
68. Wald A, Scarpignato C, Mueller-Lissner S, Kamm MA, Hinkel U, Helfrich I, et al. A multinational survey of prevalence and patterns of laxative use among adults with self-defined constipation. *Aliment Pharmacol Ther*. 2008;28:917-30.
69. Talley NJ, Holtmann G, Agreus L, Jones M. Gastrointestinal symptoms and subjects cluster into distinct upper and lower groupings in the community: a four nations study. *Am J Gastroenterol*. 2000;95:1439-47.
70. Stanghellini V. Three-month prevalence rates of gastrointestinal symptoms and the influence of demographic factors: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterol Suppl*. 1999;231:20-8.
71. Quigley EM. Impact of bloating and distention in irritable bowel syndrome: have we wandered too far from the Manning creed? *Clinical Gastroenterology and Hepatology*. 2009;7:7-8.
72. Drossman DA, Weinland SR. Commentary: sociocultural factors in medicine and gastrointestinal research. *Eur J Gastroenterol Hepatol*. 2008;20:593-5.
73. Sach J, Bolus R, Fitzgerald L, Naliboff BD, Chang L, Mayer EA. Is there a difference between abdominal pain and discomfort in moderate to severe IBS patients? *Am J Gastroenterol*. 2002;97:3131-8.

74. Zola I. Culture and symptoms: an analysis of patients' presenting complaints. *Am Sociol Rev.* 1966;31:615.
75. Lu CL, Lang HC, Chang FY, Chen CY, Luo JC, Wang SS, et al. Prevalence and health/social impacts of functional dyspepsia in Taiwan: a study based on the Rome criteria questionnaire survey assisted by endoscopic exclusion among a physical check-up population. *Scand J Gastroenterol.* 2005;40:402-11.
76. Wang A, Liao X, Xiong L, Peng S, Xiao Y, Liu S, et al. The clinical overlap between functional dyspepsia and irritable bowel syndrome based on Rome III criteria. *BMC Gastroenterol.* 2008;8:43.
77. Kleinman A, Eisenberg L, Good B. Culture, illness, and care: clinical lessons from anthropologic and cross-cultural research. *Ann Intern Med.* 1978;88:251-8.
78. Mann JJ, Malone KM, Nielsen DA, Goldman D, Erdos J, Gelernter J. Possible association of a polymorphism of the tryptophan hydroxylase gene with suicidal behavior in depressed patients. *Am J Psychiatry.* 1997;154:1451-3.
79. E M. Move Over, BRICs. Here Come the MISTs. *Bloomberg Business week, Markets & Finance.* August 9th 2012. <http://www.businessweek.com/articles/2012-08-09/move-over-brics-dot-here-come-the-mists>. 2012.
80. E M. Goldman Sachs's MIST Topping BRICs as Smaller Markets Outperform. *Bloomberg.* August 6th 2012. <http://www.bloomberg.com/news/2012-08-07/goldman-sachs-s-mist-topping-brics-as-smaller-markets-outperform.html>. 2012.
81. Sullivan PF, Jiang Y, Neale MC, Kendler KS, Straub RE. Association of the tryptophan hydroxylase gene with smoking initiation but not progression to nicotine dependence. *Am J Med Genet.* 2001;105:479-84.
82. Lara di Lauro E. El modelo de Salud en Mexico. Grupo Tecnica. Consultores y Actuarios. Una firma de Milliman Global.
83. Korean National Health Insurance Corporation. 2012. Available from: <http://www.nhic.or.kr/english/main.html>.
84. Kim KH, Park EC, Hahm MI. The gap between physicians and the public in satisfaction with the National Health Insurance system in Korea. *J Korean Med Sci.* 2012;27:579-85.
85. Bellini M, Tosetti C, Costa F, Biagi S, Stasi C, Del Punta A, et al. The general practitioner's approach to irritable bowel syndrome: from intention to practice. *Dig Liver Dis.* 2005;37:934-9.
86. Leyva-Jimenez R, Olvera-Torres P, Alvarez-Cordova MM, Alcantar-Saldivar EL. [Irritable bowel syndrome in adults attending to medical offices at UMF]. *Revista medica del Instituto Mexicano del Seguro Social.* 2006;44:473-9.
87. El Portal. 50% de las consultas de los servicios de gastroenterología son por colitis 2012. Available from: <http://elportalslp.com.mx/noticia.php?id=3314>.
88. Schmulson MJ, Remes-Troche JM, Vargas JA, Lopez-Alvarenga JC, Teramoto O, Crespo Y, et al. The severity of IBS symptoms is related to the patient's choice of different medical specialties. *Neurogastroenterol Motil.* 2010;22 (Suppl 1):59.
89. NECA (National Evidence-Based Collaboration Agency). Disease burden of irritable bowel syndrome in Korea. 2010.
90. Tosetti C, Bellentani S, Benedetto E, Ubaldi E, Cardin F, Bozzani A, et al. The management of patients with new onset of upper gastro-intestinal symptoms in primary care. *Dig Liver Dis.* 2010;42:860-4.
91. Shah SS, Bhatia SJ, Mistry FP. Epidemiology of dyspepsia in the general population in Mumbai. *Indian J Gastroenterol.* 2001;20:103-6.
92. Schmulson MJ, Valdovinos Diaz MA. [Utilization of medical resources for patients with irritable bowel syndrome in a tertiary hospital. *Rev Gastroenterol Mex.* 1998;63:6-10.
93. Ghoshal UC, Abraham P, Bhatt C, Choudhuri G, Bhatia SJ, Shenoy KT, et al. Epidemiological and clinical profile of irritable bowel syndrome in India: report of the Indian Society of Gastroenterology Task Force. *Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology.* 2008;27:22-8.



94. Banerjee R, Choung OW, Gupta R, Tandan M, Lakhtakia S, Rao GV, et al. Rome I criteria are more sensitive than Rome II for diagnosis of irritable bowel syndrome in Indian patients. *Indian J Gastroenterol.* 2005;24:164-6.
95. Ghoshal UC, Abraham P, Bhatia SJ, Misra SP, Choudhuri G, Biswas KD, et al. Comparison of Manning, Rome I, II, III, and Asian diagnostic criteria: Report of a multi-centric Indian irritable bowel syndrome (MIIBS) study. *Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology.* 2013;32:369-75.
96. Ortiz-Garrido O, Schmulson MJ. Los medicos en latinoamerica reportan utilizar con mayor frecuencia los mas recientes criterios de Roma III para diagnosticar sindrome de intestino irritable en la clinica. Pero conocen realmente los criterios? *Rev Gastroenterol Mex.* 2012;77 (Suppl 3)(95).
97. Makharia GK, Verma AK, Amarchand R, Goswami A, Singh P, Agnihotri A, et al. Prevalence of irritable bowel syndrome: a community based study from northern India. *Journal of neurogastroenterology and motility.* 2011;17:82-7.
98. Singh P, Agnihotri A, Pathak MK, Shirazi A, Tiwari RP, Sreenivas V, et al. Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. *J Neurogastroenterol Motil.* 2012;18:324-31.
99. Neri L, Basilisco G, Corazziari E, Stanghellini V, et. al. Productivity losses and health care utilization in a national sample of patients with functional constipation. 2013;In press.
100. Mateos G, Vargas JA, Crespo Y, Jiminez A, Remes-Troche JM, Lopez-Colombo A, et al. The economic burden of IBS in a Latin-American population. A report from the Mexican IBS Working Group. *Gastroenterology.* 2011;140 (Suppl 1):S1362.
101. Lahner E, Bellentani S, De Bastiani R, Tosetti C, Arullani P, Bruno Annibale B. Use of alternative and complementary therapies in functional gastrointestinal disorders: an Italian survey. *European Journal of Integrative Medicine.* 2012;Suppl 4:172.
102. Carmona-Sanchez R, Tostado-Fernandez FA. [Prevalence of use of alternative and complementary medicine in patients with irritable bowel syndrome, functional dyspepsia and gastroesophageal reflux disease]. *Rev Gastroenterol Mex.* 2005;70:393-8.
103. Kiecolt-Glaser JK, Newton TL. Marriage and health: his and hers. *Psychol Bull.* 2001;127:472-503.
104. Gerson MJ, Gerson CD. The importance of relationships in patients with irritable bowel syndrome: a review. *Gastroenterol Res Pract.* 2012;1-5:1, Article ID 157340.
105. Wong RK, Drossman DA, Lesesrman J, Hu YU, Bangdiwala SI. Irritable bowel syndrome causes increased partner burden: a comparative study. *Gastroenterology.* 2011;140 (suppl 1):S463-S363.
106. Levy RL, Whitehead WE, Walker LS, Von Korff M, Feld AD, Garner M, et al. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms. *Am J Gastroenterol.* 2004;99:2442-51.
107. Jones MP, Wessinger S, Crowell MD. Coping strategies and interpersonal support in patients with irritable bowel syndrome and inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2006;4:474-81.