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Integrating health-related quality of life into cross-national clinical trials

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When planning to implement health-related quality of life (HRQL) assessment in a multinational clinical trial, there are at least four general considerations: the natural history of the disease or condition, the characteristics of the population, the treatment under consideration, and the structure and function of the clinical trial organization. Each of these considerations must be addressed simultaneously when planning, implementing and analysing a cross-national clinical trial. There are five relevant polar components of the natural history of a given disease or condition: (1) time frame (acute *versus* chronic); (2) life threat (yes *versus* no); (3) symptomatology (present *versus* absent); (4) symptom expression (episodic *versus* constant); and (5) functional impact (present *versus* absent). Differences in population characteristics, (e.g., age, conditions, co-morbidity), embedded within any cross-national trial, must be addressed conceptually prior to initiating the trial, methodologically when planning implementation, and statistically after the collection of the data. In terms of treatment, issues such as adverse and positive effects and timing of effects must be considered. The methods entailed in planning, implementing and analysing HRQL data will depend upon the degree of centralization of personnel and resources within any given clinical trial. The range of possibilities runs from complete centralization, in which all planning and coordination of data collection and transmittal is done by one office, to complete decentralization, in which the work is distributed to participating sites and interested investigators. Finally, successful implementation of HRQL data collection is enhanced by heightening awareness of the importance of, and value in, assessing HRQL in clinical trials. The investigator embarking on a treatment trial can extend the outcome inquiry into broader areas of function and well-being than those defined by the more traditional symptom profiles, morbidity and mortality outcomes.

Key words: Health-related quality of life (HRQL), clinical trials, data collection.

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Culture influences health behaviour and perceptions by shaping explanations of sickness, social position and meaning of life.[1–4] As addressed in several papers within this issue, patients in multinational trials possess attributes that create barriers to standard health-related quality of life (HRQL) evaluation, such as, cultural diversity, different language and low literacy. By virtue of inclusion and exclusion criteria, participants in clinical trials invariably represent a select population. Thus, generality of clinical trial results is always in question. The problem extends to issues of education and economic status which vary dramatically within nations and therefore must be addressed in any trial, regardless of whether it crosses national boundaries.

When planning to implement HRQL assessment in a multinational clinical trial, there are four general considerations: the natural history of the disease or condition, the characteristics of the population, the treatment under consideration, and the structure and function of the clinical trial organization. Each of these considerations must be considered simultaneously—not hierarchically—during planning, implementation, and analysis of a trial to ensure the smooth integration of HRQL, and quality data.

Natural history of the disease or condition

In primary prevention trails, the concern is with the effects of treatment (see below) rather than the

natural history of the condition. In these situations, the investigator's selection of HRQL instruments is governed more by the trail design, effects of treatment, and population parameters. Measures designed for a healthy population are appropriate. In trials with patient populations, there are at least five relevant polar components of the natural history of a given disease or condition that are relevant to the selection of HRQL measures: (1) time frame (i.e., whether a condition is acute or chronic); (2) life threat (i.e., whether or not the condition of interest is life threatening); (3) symptomatology (i.e., whether or not there are symptoms associated with the condition of interest); (4) symptom expression (i.e., whether symptoms are experienced episodically or continuously); and (5) functional impact (i.e., the extent to which a condition has an impact upon functional status and well-being). Each of these merits attention in planning any clinical trial, and special attention when that trial crosses national, cultural and linguistic boundaries.

Time frame (acute versus *chronic).* Acute conditions resolve themselves in one of four ways: rapid resolution without return; rapid resolution with return after some period of relief (relapse); conversion to chronicity; or death. In the case of rapid resolution, relevant HRQL questions would likely surround the patient's experience of symptomatology in the short-term, and allow for comparisons between the relative impact of symptoms *versus* side-effects of treatments that might hasten resolution. When there is risk of relapse of the acute condition (e.g., gastric ulcer), a longer duration of follow-up is required even if there is rapid relief, because relapses can be frequent and occur differently depending on the treatment employed. Also, it is wise to evaluate the broader impact of acute conditions upon general functioning and well-being, as these effects can be profound.[5] If the acute problem converts to a chronic condition, the same contrast between adverse symptoms *versus* treatment side-effects remains important but is complicated by the passage of time and its introduction of problematic thinking and outcome balancing into the treatment decision. Consider the example of pain in cancer patients. Where appropriate, acute pain will almost always be treated with narcotics despite their side-effects profile. Most people will readily accept the negative effects of narcotics (e.g., sedating effect) in exchange for immediate relief. However, if the requirement for treatment extends into a prolonged period of time, the cumulative impact of sedation and constipation must be weighed against the static benefit (assuming continued pain control). The challenge to the efficacy of interventions for chronic conditions relative to acute ones is exacerbated by the reality that, by and large, treatments for acute conditions tend to be more effective than those for chronic ones. It is understandable, then, that HRQL interest has been greater in the management of chronic conditions, where there is a growing relative emphasis on morbidity over mortality. Because of the incurable nature of most chronic diseases, postponement of onset and treatment of associated symptoms may be the most relevant pursuits, which points to the primary importance of HRQL data in clinical trials dealing with chronic conditions.

Life threat. Consider a non-life-threatening intervention which is likely to favourably alter a risk factor for premature death. Survival across the entire group of patients in the study will be improved by the intervention. However, the extent of improvement must be weighed against the adverse effects of the intervention. This is particularly relevant when one considers that whereas toxicity and cost are certain, there is no certainty that an individually-treated patient will derive the benefit. The decision to take such a treatment, which carries certain side-effects and financial burdens, is one which is understandably framed by the cultural context of the patient, including personal values as they are influenced by culture and, more overtly, international variations in healthcare financing.

Symptomatology (present versus *absent).* Clearly, deciding that any intervention has value in treating asymptomatic conditions must be based upon its preventive or life-prolonging benefit. Again, such a decision is nested in the relative value of the extension of life (or compression of morbidity afforded by deferral of symptom onset) within the cultural context of the patient group. When a trial cuts across nations or cultures with different value thresholds for these benefits, it may be appropriate to stratify or separately analyse the cost-utility ratio for a given treatment across culture. Consideration must also be given to degree of side-effects associated with the preventive or life-prolonging treatment, because this will contribute to nonadherence which will likely reduce the morbidity and mortality benefit. Examples of the interrelationship between acute side-effects and deferred,

uncertain benefit can be found in prevention trials for hypertension, hypercholesterolaemia, breast cancer and prostate cancer.

Symptom expression (episodic versus *constant).* Chronic conditions with episodic symptomatic flare-ups (e.g., myasthenia gravis) can at times appear on the surface to behave more like intermittent acute conditions. One major distinction between the two, however, is that often some intervention for the chronic condition must be administered during latent (asymptomatic) periods. Also, the relief offered for many chronic conditions is not as complete as that for acute conditions which, by definition, resolve in a short period of time. If the treatment carries side-effects or adds to unrelated health risks, this then poses the challenging question of how to factor the adverse effects of treatment during quiescent periods of symptom expression into the benefits of symptom relief or prevention at a later time. As with many other issues like this which emerge in a given clinical trial, the question is further complicated by patient's value systems which may vary across cultures. It is recommended that an effort be made in multinational, cross-cultural trials to identify differences in patient values, weights or preferences for different types of symptom expression, and for different side-effect profiles. Cultural variability in symptom expression (e.g., histrionic *versus* stoic expression of pain) can be referred to within-patient values for the alternative offered by the treatment (e.g., some degree of relief with added side-effects), as a way of evaluating efficacy and circumventing the risk of cultural bias introduced by combining data across groups.

Functional impact (present versus *absent).* Kaplan[6] has argued that along with survival itself, behaviour, or the functional impact of any condition, is its most important defining characteristic. Indeed, when evaluating the effect of a condition or treatment, it is difficult to define a parameter such as a laboratory finding or prognostic indicator which should carry more weight than patient function and well-being. For conditions which have little or no adverse effect upon patient function, treatments are best evaluated on the basis of their impact on survival itself rather than intermediate endpoints presumed to be relevant unless treatment adversely effects function. In the multinational context, an added layer of complexity emerges because one must take into account different values placed upon relevant endpoints of survival time and functional impact.

When a disease or condition has some impact upon functional capacity, as is more often the case, treatments for that condition must be evaluated for their influence, both positive and negative, upon that functioning. In the context of Kaplan's[6] argument, this evaluation is rather simple if survival time is unchanged by the intervention, because one must only weight the relative cost against the relative benefit to HRQL (as both are perceived by the patient). If survival time is altered by the treatment (either by lengthening or shortening), it becomes difficult with our current technology and statistical development to go beyond descriptions of the HRQL data against the background of the survival impact. Efforts to integrate HRQL data collected from patients with survival time remain experimental, controversial and problematic for reasons that extend beyond the scope of this paper (see Revicki *et al.*[7]).

Population characteristics

Cultural bias can lead to at least three erroneous conclusions about HRQL data collected in a multinational clinical trial: (1) that there are no differences in HRQL attributable to culture (cross-cultural ignorance); (2) that there are extreme cross-cultural differences in reporting which render multinational clinical trials futile due to invalidity of conclusions (cross-cultural nihilism); and (3) that in order to be culturally sensitive, different cultures must employ different methods or instruments to evaluate HRQL (cross-cultural confusion). In reality, there are some systematic variations across cultures in terms of reporting style, illness experience, expectation from treatment, and acceptability of treatment. Often, within-country differences in a culturally-diverse nation will be more dramatic than those across culturally-similar countries.

It cannot be assumed that a well-translated instrument is cross-culturally valid by virtue of its translation. Not only may the content areas sampled be inappropriate (or at least less relevant when compared with the original instrument), but the response categories may not transfer well. For example, people in certain cultures have been said to have difficulty conceptualizing a spectrum of function or well-being depicted on a 100 mm line. Guyatt and colleagues[8] have shown that elderly

and more physically-impaired patients have difficulty conceptualizing visual analogue scales. Similarly, the distinction between commonly-used terms like 'often' and 'frequently', or between 'somewhat' and 'quite a bit', may differ across cultures. Another complication occurs when the normal expression of a symptom or concern varies systematically across cultures. If an intervention to be tested is targeted toward that symptom, then a stratification by cultural group prior to randomization should be considered in order to avoid misinterpretation of differences in expression over time. These concerns notwithstanding, many cultural and linguistic differences can be taken into account by using methods of equating measures which allow for meaningful cross-cultural comparisons of results. These techniques are discussed in detail in Bullinger *et al.*[9] and Hays *et al.*[10] in this issue.

In addition to cultural variability, a number of population-specific factors must be considered in the integration of HRQL into clinical research. The age distribution, socio-economic status, gender, clinical status and co-morbidity of the population are all relevant to the choice of HRQL measures. And, although exclusion and inclusion criteria will minimize to some degree the variability in these factors within one country, the cross-national trial introduces sources of variation in even apparently comparable indices. Differences in access to health care, for example, will influence the economic variance of study groups cross-nationally. Ascertainment and reporting of co-morbidity can also vary by cultural subgroups. With the current trend toward large, simpler cross-national trials with fewer exclusion criteria, population heterogeneity within and across countries will increase. Selecting a set of HRQL measures and data collection techniques that adequately address this heterogeneity are major challenges to the HRQL investigator.

Treatment or intervention. The planned intervention has an important influence in the selection and timing of HRQL measures. Both adverse and positive effects must be well-understood and *a priori* assumptions regarding effects should be avoided. For example, trials of behavioural interventions (e.g., smoking cessation, weight loss), are as prone to adverse effects (e.g., tension, gastrointestinal problems), as are the more traditional pharmacological interventions. Yet, investigators may assume that 'healthy behaviours' necessarily produce positive outcomes at no cost to the trial participant. This assumption can lead to inadequate coverage of relevant HRQL dimensions. This issue is exacerbated in cross-national and cross-cultural studies where norms associated with healthy behaviours may be highly variable.

The effects of treatments may vary over time. Thus, timing of the assessment of HRQL is critical. Further, this effect can also vary cross-nationally. For example, in surgical interventions (e.g., cardiac bypass surgery) length of stay in hospital varies dramatically across countries, and length in hospital can effect the patients' HRQL.

Structure and function of the organization conducting the trial. The methods entailed in planning, implementing and analysing HRQL data will depend upon the degree of centralization of the trial organization. For example, many cooperative groups have a central office which handles inter-institutional communication, traffic of forms, and other organizational functions. Data management and biostatistics may be similarly centralized. Each group of investigators must assess its ideal degree of centralization of personnel and resources. The range of possibilities runs from complete centralization, in which all planning and coordination of data collection and transmittal is done by one office, to complete decentralization, in which the work is distributed to participation sites and interested investigators. Each approach has competing advantages and disadvantages. Centralization of effort can be more cost-effective in the long run, and removes burden from the clinical site practitioners, thereby potentially enhancing quality control of data collection. On the other hand, centralization is more expensive to initiate (because a person must be hired as a centralized coordinator), it can be perceived by the patient as impersonal, and may interfere with the provider–patient relationship if the patient is not helped to appreciate the link between the treatment relationship and the value of the study being conducted. If, however, data are collected on site (decentralization), it is important to inform the patient and ensure that the information about HRQL reported on the form will not be fed back to the treating health professional. This will encourage more honesty on the form by removing the fear that treatment decisions depend upon the patient's responses. Investigators are advised to address the issue of optimal centralization of their effort within the context of their organizational structure.

Quality control: managing the HRQL component of a clinical trial. Whatever the degree of centralization, unless HRQL is the primary outcome, investigators are advised to keep questionnaire content, timing schedule, and administration instructions as simple as possible.[11–13] In this light, quality control procedures are likely to be most successful if they closely approximate existing quality control mechanisms within the trial group. Nevertheless, the need for special procedures must be acknowledged. Quality control in HRQL studies is important at all phases of the study, from protocol development, to initiation of the study, and into follow-up of patients over time. Quality control needs differ according to which point along the sequence of the study one is discussing.

Quality assurance. For any HRQL effort to succeed, quality study management is essential. Nowhere is this more true than in the complex, multi-layered, multinational setting. Some centralized person or organization must be willing to take active and primary responsibility for the management of the project. Frequent contact, including the provision of ample opportunities for open communication, is an important and effective tool to maintain both the quality and the quantity of the collected data. An electronic mail user's group with a specified mailbox name can be very useful in allowing site investigators to check on a daily basis for new information and HRQL trial updates. Also, frequent (e.g., semi-monthly) conference calls with the site interviewers or data collectors help to improve data quality by allowing less experienced personnel the opportunity to go over any questions or problems, and to obtain an update on their accrual, comparing it with their target accrual.

Recently, the Canadian National Cancer Institute reported impressive quality control of HRQL data on three of its trials, with overall compliance ranging from 95–99%.[14] These trials included English and French (and in one case, Italian) speaking patients. They describe nine specific measures which contributed to their success:

- Making quality of life a specific (i.e., mandatory) trial objective;
- Providing a clear rationale for studying HRQL in the protocol document;
- Including HRQL administration instructions in the protocol document;
- Modifying data collection forms to remind data managers to gather data;
- Providing specific reporting schedules;
- Establishing successful completion of the HRQL as a prerequisite of eligibility with verification of questionnaire completion at the time of randomization;
- Providing computer-based reminders in advance of the due dates for questionnaire completion;
- Providing pretrial workshops for data managers on HRQL rationale and administration procedures;
- Providing ongoing feedback to participants via letter and newsletter.

All of these procedures can easily be applied to most multinational trials with minimal effort, as long as they have the support of the leadership of the clinical trial organization and of the study chairs.

Protocol development. There are two issues related to protocol development that surface prior to any HRQL study activation. First, the usual review process, in which study investigators and institutional principal investigators, and biostatisticians examine the protocol, is inadequate for HRQL studies. The reason for this is the fact that data collection will require the learning of unfamiliar techniques by nurses and data managers. Therefore, protocol input from these disciplines, as well as from collaborating social scientists, is necessary in order to clarify any misunderstandings before they complicate the study procedures. It is important to establish that all disciplines are aware of each others' responsibilities within a particular HRQL study; and this can be specified in the written protocol.

A second issue related to protocol development is the shortage of specialized expertise in statistical handling of multidimensional, correlated data collected at multiple time points. Statisticians in cooperative groups are typically confronted with unprecedented difficulty managing and analysing data such as these. It is important to clarify analytic plans *prior* to initiating a study.

Sampling considerations. Random or even truly representative samples are rarely attainable. One must usually identify an available study population and decide upon inclusion and exclusion criteria. Unless everyone will be seen, a selection strategy for eligible patients is needed. Without

such a strategy, the sample will likely be reduced to one of convenience. This approach can bias study conclusions because results could be confounded by some factor which is correlated with the selection method. For instance, a telephone study using a sample of convenience at home may over-represent phobic, withdrawn or debilitated patients who are more likely to be there to answer the phone.

Timing of measurement. Consideration of timing is deceptively complex. Detailed recommendations can be found elsewhere.[15] When determining the specific assessment times, the investigator must balance treatment toxicities, the natural history of the disease, and time since initiating new therapy along with a constant awareness of the study objectives. An additional level of complexity is added when comparing treatments of differing lengths with one another. The investigator is encouraged to consult with other colleagues who have experience with these treatments in order to catch any 'blind spots' in planning these times that could render the comparison unfair. Finally, it is important to remind the investigator that patients should continue to be assessed for their HRQL even if they discontinue therapy for some reason. A proposal for tracking down and studying these patients if they become lost to the institution should be specified.

Implementing HRQL assessment. Although the details of implementation are of equal if not greater importance compared with the choice of instrumentation, the latter issue receives far more attention when planning the typical clinical trial. Whereas the task of instrument choice is completed before the trial begins, the task of implementation continues throughout the course of the trial. Unsuccessful implementation threatens the conclusion validity of the trial at many levels, including sampling bias (if all patients or a random subset do not participate), generalizability (if all institutions or cultures do not participate), and statistical conclusion validity (if there are missing data or inappropriate analyses planned).

Because of the unique nature of HRQL data, staff and patients will require pre-study education and/or training about the nature of the HRQL investigation, its purpose and its procedures. This can be a labour-intensive effort which requires central coordination and planning. As the study progresses, busy clinical schedules, normal staff turnover, and lack of accountability can all contribute to systematic forgetting about the HRQL component of the study over time. The result is patient attrition. Even if the protocol is carefully conceived, written and executed at study initiation, there remains a need for continued vigilance toward the risk of obtaining a declining rate of participation. Planned 'booster' educational sessions and enforced accountability at each data collection site are mechanisms that can be considered to enhance quality control during follow-up.

Training and monitoring interviewers. The conclusions drawn from multinational HRQL studies will have significant implications for the interpretation of medical outcomes and patient preferences. Patients must be helped to feel as comfortable as possible, thereby maximizing the likelihood that they will provide veridical data. It is therefore important that interviewers be perceived as members of a similar culture to the extent possible, in order to set patients at ease and facilitate removal of status barriers between examiners and respondents. HRQL measures are all fairly easy to administer, provided that a minimum degree of preparatory training and monitoring occurs. Some standardization of administration must be established and monitored during the course of the trial. For inexperienced data collectors, an initial pilot study could offer the opportunity for experience-based training which, when appropriately monitored, will improve consistent administration technique. The procedure for administration of the HRQL battery can also be standardized in a brief training manual or guide. Administration guidelines specific to the instrument to be given and the trial to be conducted should be provided whenever necessary. Standardized aspects of test administration must be consistently addressed at each site, and this is best monitored centrally after initial training.

Local procedures for approaching, studying, and tracking patients

With an organized effort at the local institution level, high quality data collection can occur. It is important to remain aware that HRQL data differ from other trial data in two fundamental ways. First, they are obtained directly from the patient and therefore necessitate enlisting patient cooperation beyond that required for treatment adherence. Second, they cannot be retrieved from medical

records if they are not measured at the specified time. This means that the on-site responsible person is vital to the successful completion of all HRQL protocols. This person must be motivated and able to stay abreast of upcoming patients who must complete the HRQL form. Quality assurance procedures must be specified in the protocol and carried out on-site.

Specific recommendations. It is recommended: (1) that each participating institution designate a person who has responsibility for the HRQL component of the study; (2) that each institution has a plan for keeping track of when HRQL data are due on each individual patient; and (3) that the institution has a plan for promptly contacting patients who miss an assessment appointment. An acceptable window of time should also be specified after which data must be considered irretrievable. Procedures for this retrieval, including acceptable methods of data collection (proxy informant, mail, telephone, etc.), should be specific before beginning the trial.

When the patient begins to complete the HRQL form, remind him or her of the time-frame specified on the questionnaire (e.g., 'past week'). If the patient requires assistance completing forms, this can be provided by the responsible HRQL representative (who has been trained to provide assistance without introducing bias), or a comparably trained staff person, but not by family or friends of the patient. After the patient completes the HRQL form, it should be checked for completeness and accuracy. If items are left unanswered or if the responses are made incorrectly (e.g., circling a descriptive word when in fact a number was to be circled), they should be presented back to the patient with a request for clarification. If the patient does not want to answer, an explanation to this effect should be written in the margin and submitted to the data management office for study.

Institutional tracking and quality assurance. A suggested way to keep track of patients is to assign two 'cards' to each patient. These 'cards' may take the form of two different sorts in a spreadsheet computer program, or they can be actual index cards in a filing box. One card is sorted according to the date 2 weeks before the participant is due to complete the next HRQL evaluation. This card also contains the patient's name and phone number, the treating physician's name and phone number, and the study identification number. The other card is sorted alphabetically, and contains the location (i.e., date in file) where the other card can be located. This cross-referencing enables one to both stay abreast of who should be receiving HRQL evaluations in a given week and when any given patient is due for an HRQL evaluation. This ensures against loss of contact and greatly improves the likelihood that a patient will arrive within the window of time required by the protocol.

Before the patient's next visit, a parameter sheet describing which tests are required for the visit should be checked. If an HRQL evaluation is among them, the patient can be called and prepared for this approximately 1 week prior to the appointment date.

Access to patients. Gaining access to patients may be a significant issue when assessing HRQL. Although there may appear to be adequate numbers of patients or families in a particular setting, some studies languish due to accrual problems. This may be a sign of resistance. Where low accrual is due to a poorly motivated staff, efforts to enhance their interest and commitment to participation, perhaps with built-in incentives, are important. For the patient, an HRQL evaluation must be placed in a context so it is not perceived as gratuitously intrusive. Piloting can determine acceptability to patients and families, and written consent can prepare them for the nature of the inquiry.

Additional concerns

In addition to the issues addressed in the preceding pages, there are several aspects of a clinical trial that impinge upon the smooth integration of an HRQL assessment. These include: whether or not the trial is masked (blinded), the duration of the trial, the methods for participant debriefing, responses to untoward events, whether or not HRQL data are to be factored into stopping rules, and whether or not cut-off scores in HRQL are used for referral.

In terms of trial duration, HRQL investigators must consider the frequency of HRQL assessment over time and if aspects of HRQL could change with time, independent of the treatment or the natural history of the condition. For example, in the recently initiated Women's Health Initiative in the United States, 9+ years of follow-up is planned

in this multi-cultural study. It could be argued that specific aspects of HRQL, ranges of HRQL within specific dimensions, or terms used to describe aspects of HRQL could change with time and within culture. This potential 'drift' in meaning or measurement should be assessed periodically throughout the course of the trial.

HRQL data are rarely if ever used in stopping rules, though this may change as these measures become more precise and more accepted as standard indices of treatment efficacy. However, cut-off scores on HRQL measures have been used for patient referral. For example, patients' scoring high on indices of poor mental health may be referred for counselling, just as patients with high blood pressure or arrhythmias would be referred. Thus, the importance of cross-cultural comparability in meaning and range of scores becomes even more critical since differences could lead to variations in referral practices by clinic site.

Conclusion

In this paper we have outlined some of the key issues involved in implementation of quality of life investigation in multinational clinical trials. We provide guidelines and recommendations regarding dealing with the natural history of the disease or condition in question, consideration of the characteristics of the population, treatment issues, and successful implementation in the context of the organization conducting the trial. Successful implementation of HRQL data collection is enhanced by heightening awareness of the importance of and value in conducting HRQL studies within clinical trials. Planning a successful quality of life evaluation in a clinical trial setting is like a 'balancing act.' The researcher must weight the advantages and disadvantages of competing approaches and measures. For example, what may be sacrificed in comprehensiveness of measurement may be gained in response rate. The investigator embarking on a treatment trial can extend the outcome inquiry into broader areas of function and well-being than those defined by the symptom profile of the condition being treated. The decision to do this increases the chance that relevant improvement in the overall functioning of the patient, or decrements attributable to treatment, will be detected. By acknowledging the relationships among physical, social and mental health, HRQL evaluation also makes more valid the understanding of the total costs and benefits of a given treatment.

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