Japan Clinical Oncology Group

Policy No. 30
Title: PRO/QOL research
Applicable scope:
Study Group, PRO/QOL study coordinator, Protocol Review Committee, Data Center/Operations Office

Patient-Reported Outcome/Quality of Life (PRO/QOL) Research

1. Current situation and background

1.1. Current situation of PRO/QOL research in cancer clinical research

Previously, results obtained from clinical trials have been analyzed and new treatment methods have been provided based on scientific grounds by evaluating the safety and efficacy using objective endpoints in cancer treatment development. However, a movement favoring the promotion of patient-focused drug development has been spreading mainly in Europe and the U.S. that would reflect the opinions, experiences, and preferences of patients actually being treated.[1] The U.S. Food and Drug Administration (FDA) published a guidance[2] in 2009 that summarized points to note when using PRO/QOL as an endpoint in treatment development; in Europe, the European Medicines Agency (EMA) published a guidance[3] for evaluating health-related QOL (HR-QOL) in 2005 and a revised edition in 2016.[4]

The Japan Clinical Oncology Group (JCOG) has aimed to improve the quality of medical care and treatment outcomes for cancer patients by establishing new, highly effective standard therapies through multicenter clinical trials. To achieve this end, clinical trials have been implemented that preferentially adopt exceptionally reliable and objective endpoints, including overall survival. However, there has been an increasing demand from JCOG researchers for the use of PRO/QOL, whereby patients conduct self-reported evaluations of the treatment they have received in a clinical trial as a secondary endpoint. This situation resulted in the formation of the former QOL *ad hoc* committee, which deliberated about the conditions for using PRO/QOL in clinical trials conducted by JCOG (hereafter, JCOG trials) and created the former version of the QOL Assessment policy (hereafter, the former QOL policy) approved on January 18, 2006.

However, when using PRO/QOL as an endpoint, there are also issues regarding data handling, reliability, and scientific aspects of the data, including the lack of standardized methods for dealing with missing values for patients whose conditions have deteriorated and statistical analysis methods for processing the results obtained. Furthermore, PRO/QOL research creates an extremely large burden for JCOG researchers and the Data Center for tasks such as data collection, thus resulting in limited PRO/QOL research in JCOG trials. Although PRO/QOL was adopted as an endpoint in only nine of the 105 trials conducted by JCOG after the creation of the former QOL policy, the collection proportions for PRO/QOL survey forms, which was previously a cause for concern, were relatively good (approximately 90%), so the environment for PRO/QOL research has gradually improved in JCOG trials.

1.2. Background for establishing a PRO/QOL research Ad hoc committee and revisions of the former QOL policy

As stated previously, there has been limited PRO/QOL researches in JCOG trials. However, recently, patient and public involvement (PPI) in cancer treatment development has been promoted mainly by the Ministry of Health, Labour and Welfare, and incorporating PRO/QOL

assessments into cancer clinical trials is once again attracting attention. JCOG is also now of the opinion that it is necessary to reconsider the position of PRO/QOL research in its trials with the groundswell of support for promoting PPI in cancer treatment development and the deepening of cooperative research and human exchange with the European Organisation for Research and Treatment of Cancer (EORTC), which has led PRO/QOL research in cancer since 1980. The EORTC-JCOG PRO/QOL Workshop was held on September 1, 2018, providing an opportunity to further promote this movement[5]. After deliberating on the topic in this workshop (refer to Introduction to Clinical Research (ICR) web; EORTC-JCOG PRO/QOL Workshop 2018 https://www.icrweb.jp (lectures were given in English)), it was considered necessary to revise the former QOL policy to promote PRO/QOL research in future JCOG trials, resulting in the formation of the JCOG PRO/QOL research *ad hoc* committee (March 2019).

2. Purpose

The purpose of this policy is to define JCOG's PRO/QOL research and present the guidance when using PRO/QOL as an endpoint in JCOG trials.

3. Glossary

The terminology used in this policy is explained below.

- **PRO (Patient-Reported Outcome)**: Refers to clinical research outcomes for which patients evaluate their diseases and treatments; other people (e.g., doctors) do not add a separate interpretation to patient evaluations.
- **QOL (Quality of Life)**: QOL is a term that expresses the overall quality of a person's lifestyle and life, including multiple factors, such as physical, psychological, and social perspectives; QOL covers not only patients but also healthy individuals, as described in the WHO's definition of health.
- **HRQOL (Health-related Quality of Life)**: HRQOL limits the scope of evaluation to areas of QOL that are affected by disease or can be expected to improve through medical treatment. Therefore, the QOL measured in cancer clinical trials is HRQOL, and the QOL in this policy means HRQOL. ※

※ Some people consider HRQOL as part of PRO, so there is room for debate regarding this definition. In this policy, both PRO and HRQOL are distinguished based on different perspectives: PRO looks at how one measures, whereas HRQOL looks at what one measures (Table).

Table: Relationship between PROs and HRQOL in this policy (the shaded part is the applicable scope of the policy)

	PRO	Non-PRO
HRQOL	When patients evaluate/respond using a QOL scale containing multiple domains※ Example: When patients answer the EORTC QLQ-C30, FACT-G, EQ-5D, etc.	When persons other than the patients evaluate/respond using a QOL scale containing multiple domains Example: When parents answer on behalf of children regarding pediatric diseases
Non-HRQOL	When patients evaluate symptoms and/or adverse events Example: PRO-CTCAE	When the medical staff evaluates patient symptoms and/or adverse events Example: ECOG PS, CTCAE

※ Refer to the following terminology for domain-related terms.

- **Psychometric properties**: The properties whereby the scale (questionnaire) used to measure QOL properties has been evaluated beforehand to ensure the quality of the scale. These are broadly classified into four properties: reliability, validity, responsiveness, and interpretability, as described below:
  - Reliability: The extent to which the measured values do not contain errors
  - Validity: Whether the item that the scale aims to measure is actually measured
  - Responsiveness: The ability to detect change over time
  - Interpretability: The extent to which qualitative meaning can be given to the evaluation results
- **Domain**: The elements that comprise the concept of QOL, including activity, physicality, spirituality, and sociality. Typical QOL questionnaires—the EORTC QLQ-C30 and FACT-G—are comprised of multiple corresponding questions to evaluate each domain.
- **Recall period**: The period of time in which subjects is asked to remember (recall) when responding to the questionnaire (e.g., “Please circle only one number that best fits your condition in the past week”)
- **Minimally important difference (MID)**: The minimal clinically meaningful difference in QOL evaluations
- **Scale**: A tool such as a question sheet, questionnaire, or subject diary used to measure symptoms and function
- **Subscale**: Scales specific to disease, tumors, symptoms, and/or treatment (e.g., breast cancer: EORTC QLQ-BR23; head and neck cancer: EORTC QLQ-H＆N43), in addition to general scales (e.g., EORTC QLQ-C30) to evaluate the QOL of cancer patients. Such specific scales are called subscales.
- **Linguistic validity**: Typical QOL questionnaires such as the EORTC QLQ-C30 and FACT-G have been translated into Japanese from English. The purpose of translation is to reproduce a questionnaire that is equivalent to the original through appropriate procedures. Important elements for equivalence in translation are conceptual equivalence, semantic equivalence, substantive equivalence, and characteristic equivalence.

4. Role of the Committee

The role of the Committee when PRO/QOL research is conducted in JCOG clinical trials is as follows:

- Providing advice on matters such as appropriate questionnaires, survey intervals, data collection methods, selection and definition of endpoints, and statistical analysis methods for JCOG trials planning PRO/QOL assessment
- Reviewing protocol including PRO/QOL assessment
- Providing advice on interpretation of analysis results and reporting of JCOG trials in which PRO/QOL assessment was conducted
- Revising PRO/QOL Research policy as needed (Chapter 8)

5. PRO/QOL research definitions

PRO/QOL research in this policy refers to research in which outcome is measured and evaluated using validated PRO/QOL questionnaires and analyzed by generally accepted scientific methods, as shown below. Research not meeting this definition is not referred to as PRO/QOL research in JCOG and is excluded from the scope of this policy.

5.1. Questionnaires used in the research

The questionnaires used in the research are to be filled-in or input by patients. Many PRO/QOL questionnaires have been used in the field of oncology for both general PRO/QOL assessments and disease- or treatment-specific evaluations, but the questionnaires used for research must have confirmed psychometric properties of reliability, validity, and responsiveness listed in the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) checklist.[6] Furthermore, when using the Japanese version of questionnaires originally created in English, they must have had scale equivalence confirmed during the translation process.

The EORTC Translation Manual[7] is available as a reference for the translation process.

5.2. Questionnaire collection methods

The questionnaires are collected by data coordinating center (JCOG Data Center, PRO/QOL Study Coordinator for each trial, etc.) established for each individual PRO/QOL research to ensure that the questionnaires are not seen by the attending physician at the participating site.

Whether using paper-based questionnaires (paper and pencil type) or electronic collection tools (ePRO: electronic Patient-Reported Outcome), appropriate staff members—including the attending physician and clinical research coordinator (CRC)—explain to patients the methods for filling-in the questionnaires or inputting information therein. Assistance with completing or inputting may be provided by appropriate staff other than the attending physician.

6. Managing PRO/QOL research

6.1. Trials including PRO/QOL assessment and the design of those trials

When planning a clinical trial that includes PRO/QOL as an endpoint, the rationale set for the endpoint and hypothesis based on that rationale should be described in advance in the study protocol, as is the practice in other clinical trials, to ensure the scientific validity of conducting PRO/QOL assessment in the relevant trial.

Blinded randomized controlled trials are the most appropriate when using PRO/QOL as an endpoint because the efficacy of the investigated treatment method and any associated adverse

events affect the patient's PRO/QOL assessment. However, in practical terms, blinding is often difficult because of the nature of the cancer treatment, and when conducting group comparisons regarding treatment, evaluation by the medical staff is not always more accurate than PRO/QOL (which is the patient's own evaluation). In fact, it has been shown that medical staffs tend to underestimate adverse events.[8] Based on this information, adopting the PRO/QOL as an endpoint is also acceptable in randomized controlled trials, including open-label trials.

The PRO/QOL assessment in a single-arm clinical trial is permitted, providing that the purpose of the trial is to investigate the feasibility of the evaluation and obtain basic data on the PRO/QOL assessment in subsequent randomized controlled trials.

6.2. Points to note when developing the study protocol

SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)[9] was published in 2013 as guideline for developing protocols for intervention studies. The SPIRIT-PRO (Standard Protocol Items: Recommendations for Interventional Trials Patient-reported Outcomes) extension[10] was published in 2018 based on the original SPIRIT as guidelines for developing protocols using PRO/QOL as an endpoint. Generally, clinical trials using the PRO/QOL assessment are planned in accordance with SPIRIT-PRO. SPIRIT-PRO has added a total of 16 items: 11 items (Extension) with added content to conform to the PRO/QOL assessment and five items (Elaboration) with detailed descriptions of the 33 items proposed in the SPIRIT guidelines. The following is an edited checklist of points to note when developing a clinical trial protocol using PRO/QOL as an endpoint based on SPIRIT-PRO.

Checklist

It is preferable to include the following when creating a protocol with PRO as an endpoint:

- ☐ Specify the individual(s) responsible for the PRO content of the trial protocol (PRO research secretariat).
- ☐ Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies
- ☐ State specific PRO objectives or hypothesis for the PRO assessment.
- ☐ Describe detailed information on the PRO scale used in the trial (e.g., target population, number of questions, recall period, and constituent domains).
- ☐ Indicate whether the PRO scale used in the trial has appropriately investigated psychometric properties and cite guidelines for interpreting the results and prior literature on patient tolerance and burden, if available.
- ☐ Describe the process for creating the Japanese version (linguistic validity).
- ☐ Summarize PRO data in prior research.
- ☐ Describe eligibility criteria specific to the PRO assessment (describe exclusion criteria based on cognitive function, language ability, and reading comprehension, if applicable).
- ☐ Describe the timing, interval, and frequency of the PRO assessment; state the rationale for setting these items, and if PRO assessment is not conducted before randomization, state the reason.
- ☐ Describe an outline of data collection procedures and state the input method (e.g., paper, telephone, electronic media) and input location (e.g., hospital, home, other).
- ☐ Describe the rules for events that may affect PRO data and describe the order and timing of PRO data collection (the results of observation by doctors, blood tests, and imaging can affect PRO data, so it is preferable to unify these events in the target population).
- ☐ Indicate the order for evaluation when using multiple questionnaires.
- ☐ Does the protocol include descriptions of the results, scoring method, score evaluation method, analysis method, and timing of main data collection?
- ☐ If a user manual on measurement methods is available, conduct measurements in accordance with the manual. If the manual is not followed, state the reason.

- ☐ When PRO is the primary endpoint, describe the required sample size and rationale for setting the sample size and analysis set (including the percentage of cases expected to be lost to follow-up during the follow-up period). When PRO is used as a secondary endpoint, describe whether the planned sample size may maintain the required power to confirm the hypothesis of the PRO/QOL research. When it is difficult to set the sample size in advance, describe the statistical power of the primary analysis.
- ☐ When conducting a clinical trial using PRO as a secondary endpoint and when collecting PRO data from only some of the target population (of the main study), state the rationale and methods.
- ☐ Describe handling of missing data and the possible effect on the results.
- ☐ Describe PRO data collection methods and data management methods devised to minimize missing data.
- ☐ Describe handling of PRO data when the target patients complete the protocol treatment or deviate from the protocol.
- ☐ Describe measures for multiple statistical tests and increased α error.
- ☐ Indicate whether the PRO data will be regularly monitored during the trial period. In these instances, describe handling with standardized methods and the methods used to explain to subjects (e.g., patient information sheet, consent form).

It is preferable to also reference SPIRIT and the guidelines for interventional trial reports: CONSORT-PRO.[11]

6.3. Handling as an endpoint

PRO/QOL is generally used as a secondary endpoint. Using PRO/QOL as the primary endpoint in studies with limited subjects and study design is a topic for future consideration.

Studies with “limited subjects and study design” include those targeting patients with advanced or recurrent cancer for which the main treatment is for symptom relief or studies aimed at the development of palliative treatment. There are actually a large number of clinical studies that have used PRO/QOL as the primary endpoint for the development of palliative radiotherapy. For example, many confirmatory trials on palliative radiotherapy for painful bone metastases have calculated the percentage for pain relief using the numeric rating scale (NRS) as the primary endpoint.[12,13] Many confirmatory trials on palliative radiotherapy for dysphagia in esophageal cancer have used the severity of dysphagia based on the PRO assessment as the primary endpoint.[14,15]

On the other hand, there are almost no reports of using PRO/QOL as the primary endpoint in cancer clinical trials to confirm the efficacy of new treatments. The results of a systematic review of phase III trials for recurrent prostate cancer published between 2000 and 2015 found that only 22.5% of the trials included PRO/QOL assessments, and no trials used PRO/QOL as the primary endpoint.[16] However, Wilson et al. described the importance of the PRO/QOL assessment and concluded that it could be set as an appropriate endpoint depending on the trial target and purpose.[17] The above information does not rule out the possibility of using PRO/QOL as the primary endpoint.

6.4. Questionnaires

Questionnaires should be selected based on the purpose of the study, psychometric properties, patient background, and other factors. Consideration should be taken to ensure that the time required to complete a questionnaire is no more than 20 minutes for the baseline assessment and no more than 10 to 15 minutes for a subsequent assessment to avoid overburdening the patient.[18] Additionally, the linguistic validity of Japanese versions of questionnaires used in the trial must be confirmed.

6.4.1. Examples of questionnaires

The following are examples of questionnaires widely used in cancer clinical trials that have been translated into Japanese:

1) EORTC Quality of Life Questionnaire (EORTC QLQ-C30)

This questionnaire is a 30-item form comprised of five domains (five items on physical functioning, two items on role functioning, two items on cognitive functioning, four items on emotional functioning, and two items on social functioning) and symptom scales (three items on fatigue, two items on nausea/vomiting, two items on pain, one item on dyspnea, one item on insomnia, one item on appetite loss, one item on constipation, one item on diarrhea), one item on financial difficulties and two items on global health status/QOL. In addition to the core questionnaire (C30), additional subscales for different types of cancer are also available, including the LC13 (lung cancer), BR23 (breast cancer), and HN43 (head and neck cancer). The recall period is one week.

When using this questionnaire for research, it is necessary to preregister via the following URL and obtain permission for use: https: //qol.eortc.org/questionnaires/

2) Functional Assessment of Cancer Therapy-General (FACT-G)

This questionnaire is a 27-item form comprised of four domains (seven items on physical well-being, seven items on social/family well-being aspects, six items on emotional well-being, and seven items on functional well-being). Several different types of additional subscales are also available for different types of cancer and for treatment/symptom-related questions, including B (breast cancer), L (lung cancer), and Taxane (taxane anticancer drugs toxicity survey). The recall period is one week.

When using this questionnaire for research, it is necessary to preregister via the following URL, and obtain permission for use: https: //www.facit.org/FACITOrg/Questionnaires

3) MD Anderson Symptom Inventory (MDASI)

This is a scale that evaluates 13 symptoms that are quite common in cancer patients (pain, fatigue, nausea, sleep disturbance, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness). It includes six items on impediments to daily life (activity of daily living, mood, working including housework, relations with other people, walking, enjoyment of life).

Symptoms are evaluated on an 11-point scale (0 – 10). The recall period is 24 hours.

When using this questionnaire for research, it is necessary to preregister via the following URL and obtain permission for use: https: //www4.mdanderson.org/symptomresearch/index.cfm

4) Edmonton Symptom Assessment System (ESAS)

This is an evaluation sheet developed to play a role in the assessment of nine symptoms (pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, well-being). The severity of symptoms is evaluated on an 11-point scale (0–10).

Permission is not needed to use this evaluation sheet. See the following URL for details: https: //www.ncc.go.jp/jp/ncce/clinic/psychiatry/040/ESAS-r-J.pdf

5) PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The PRO version of the CTCAE was developed by the U.S. National Cancer Institute (NCI). There are 124 questions consisting of 78 items regarding adverse events.

A Japanese version has been created by Yamaguchi et al. and is available for download free-of-charge from the JCOG website. Refer to the following link:

https: //healthcaredelivery.cancer.gov/pro-ctcae/pro-ctcae_japanese.pdf

6) EQ-5D

This is a comprehensive evaluation scale developed by the EuroQol group. It is comprised of two parts: questions on five items and a visual analog scale, and they can be converted to a standardized utility value of “Completely healthy = 1” and “Dead = 0,” based on the response results. An individual’s quality-adjusted life year (QALY) can be determined with this scale, and it is used for medical economics evaluations.

When using this questionnaire for research, it is necessary to preregister via the following URL and obtain permission for use: https: //euroqol.org/

6.4.2. Assessment method and data collection

1) Assessment interval

The timing and frequency of the PRO/QOL assessment should strike a balance between the purpose/significance of the study, feasibility, and burden on the patient. This is an important issue. Investigate survey timing while considering the following items.

- The natural course of the disease: the timing of survey should correspond to the (expected) greatest changes in patient symptoms and QOL during the course of the disease.
- Hypothesis to be confirmed
- Data analysis method: comparison with baseline, time-to-event, etc.
- Characteristics of study treatment: for pharmaceuticals, consider factors such as the dose and how long the effect will be maintained after treatment.
- Recall period in the questionnaire: how far back in time will patients be required to evaluate their conditions?
- Patient burden: frequent surveys create a burden for patients and can also affect their willingness to participate in the trial. Ensure that the questionnaires do not overburden patients.

2) Assessment duration

It is recommended that the expected onset of symptoms and toxicity be considered so that data can be collected during a period that will cover the most clinically important time.

It is important to conduct evaluations continuously after a patient’s condition worsens and during the post-treatment period to ensure an accurate PRO/QOL assessment of the protocol treatment. For example, in a randomized controlled trial, the standard treatment group would be expected to have a shorter time until worsening of the primary disease than the study treatment group. In these instances, stopping PRO/QOL assessments simultaneously with a worsening of the primary disease may result in an overestimation (or underestimation) of PRO/QOL in the standard treatment group.

Based on the above information, sufficiently long assessment duration should be specified in the protocol of each study while considering feasibility and interpretability to ensure accurate evaluation of the results of PRO/QOL research.

3) Data collection method

Data collection methods include interactive voice response (IVR) and self-administered surveys (patients complete a paper survey or use electronic device). Select an appropriate collection method considering the feasibility based on the age distribution of the target patients, disease, and staging, as well as the introduction cost.

6.5. Statistical considerations

6.5.1. Statistical analysis in PRO/QOL research

Most of questionnaires, including QOL scales, are multidimensional and can generate multiple scores (e.g., score for each domain, total score). Furthermore, a PRO/QOL assessment is normally conducted at multiple points in time. Graphic display of PRO data is important, and statistical analysis should be clearly specified in the protocol written before the research begins. PRO endpoints include the score itself and responder/non-responder status (the definition is important; e.g., a 33% reduction in the score) at a specific time point, time to a specific event (e.g., a two-point reduction in the score), and change in the score and area under the curve (AUC) throughout the entire observation period. It is also necessary to consider a minimally important difference (MID; See 3. Glossary). Multiplicity issues may need to be considered at the design, analysis and interpretation steps of the research.

6.5.2. Handling missing data

Missing data inevitably occur in PRO/QOL assessments. The first consideration is developing study protocol that will minimize missing data. It is also preferable to apply analytical methods for which missing data are unlikely to affect the conclusion or analytical methods that fully consider the reasons for the missing data. Therefore, a protocol should be formulated that will collect and enable to understand reasons.

There are two levels of missing PRO/QOL data at a specific time point: (1) data are missing for some items, but not for all items in the scale, and (2) the entire PRO/QOL assessment has not been conducted.

In case of (1), methods for dealing with missing items are shown in some scale scoring manuals (e.g., methods for calculating the entire score), but it is necessary to thoroughly confirm whether application of these methods is appropriate.

In case of (2), it is necessary to make an assumption regarding the reason for missing data in the analysis (i.e., make an assumption about the missing data mechanism). There are various statistical approaches, including a complete case analysis, a number of imputation methods, and model-based methods, but it is necessary to summarize the missing status for each time point and to conduct a statistically valid analysis under the primary missing data assumptions. It is essential to thoroughly specify the methods used to deal with missing data in the protocol. Unfortunately, no universally applicable methods of handling missing data can be recommended. An investigation should be made concerning the sensitivity of the results of analysis to the method of handling missing data, especially if the number of missing data is substantial.

6.6. Reporting results

When a clinical study including a PRO/QOL assessment has been conducted, publication of the evaluation results may affect the results of the primary analysis of the study; generally, the results of the PRO/QOL assessment should be published at the same time of or after publication of the primary analysis results of the study.

When reporting the PRO/QOL assessment results of a randomized controlled trial, include information on the reproducibility and validity of the questionnaires used in the study, the methods used for the statistical analysis of the PRO/QOL assessment results, and the methods for handling missing data in accordance with CONSORT PRO Extension.[10]

7. Required resources and methods for PRO/QOL assessments

When conducting PRO/QOL assessments, the research group is required to prepare the necessary resources to achieve the following objectives:

- Conduct a baseline PRO/QOL assessment before randomization or before starting treatment on all patients who are the subjects of the PRO/QOL assessment
- Conduct the minimized PRO/QOL assessment after the start of treatment as much as possible to investigate the hypothesis for PRO/QOL, except in unavoidable cases, such as patient death, deterioration of the patient's general condition, hospital transfer, and patient refusal

The following procedures are implemented for the attending physicians and PRO/QOL data collection assistants in the participating sites as the necessary information received from data coordinating center (JCOG Data Center, etc.) and EDC systems which are built and operated by the data coordinating center:

- Send a reminder about conducting the baseline PRO/QOL assessment immediately after receiving notification of the patient registration in each trial.
- Send a reminder by email when the scheduled time for the assessment is approaching to ensure that the PRO/QOL assessment is conducted at an appropriate time after start of treatment.
- Ascertain whether the PRO/QOL assessment has been conducted at an appropriate time after when the scheduled time of the survey and send a reminder or feedback if it is suspected that the survey might have been forgotten or if there were omissions.

Because a full-time person is needed to perform these procedures indicated above, the research group must either appoint a PRO/QOL Research Coordinator within the group for each trial or outsource the duties to JCOG Data Center by providing the necessary expenses.

8. Policy revision

This policy will be revised as needed, such as when new findings are acquired that should be included herein.

9. References

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