Standardization of Quality of Life Core Outcomes in Stem Cell Clinical Trials

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ABSTRACT

Standardization of Quality of Life Core Outcomes in Stem Cell Clinical Trials

By Dori Naerbo, Ph.D.

Background: Establishing standardized Quality of Life (QOL) core outcomes in stem cell clinical trials is important to ensure (1) researchers and clinicians can make informed decisions, and (2) clinical trials use and consistently measure the same units (Clarke, 2007; Thornley & Adams, 1998). This study reviews the most common QOL methodologies, timing/frequency of the measurement, and outcomes in cardiovascular stem cell clinical trials.

Methods: To identify instruments, the study reviewed MEDLINE, Scopus, and US Clinical Trials Register through September 2010, and randomized BMSC controlled trials of clinical trials from 2000-2011. The trials all used the terms (bone marrow stem cell AND quality of life OR heart OR cardiac) AND cardiac AND quality of life OR QOL. The study included a Likert scale web-based questionnaire comprised of eight questions designed to assess QOL patient satisfaction post cardiovascular stem cell treatment.

Results: Of the instruments identified, the study found that bone marrow stem cell (BMSC) clinical trials used 35 different types of methodologies, whereas cardiovascular BMSC employed more consistent methodologies. Timing, frequency, and baseline were consistently measured in BMSC clinical trials, whereas cardiovascular BMSC lacked baseline consistency and were measured primarily after treatment. Cardiovascular BMSC outcomes were consistent, whereas BMSC clinical trials had multiple outcomes.

The mean participant age was 56.25 years with a minimum age of 46 years and a maximum age of 61 years. Participants generally were educated with a minimum education level of an Associate degree and a maximum degree of Doctorate. The patient satisfaction survey revealed that participants preferred yes/no questions and surveys that required less than 15 minutes to complete, received via email, easy to understand, not too personal, relevant to feelings, containing a baseline measure, and medical-condition specific.

Conclusion: QOL outcomes are rarely assessed in BMSC cardiovascular trials. Treatments are performed all over the world, and no one knows whether these treatments actually are effective. Both standardized measurements and additional studies are needed.

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ABBREVIATIONS

ADL	Activities of Daily Life
AHA	American Heart Association
AMI	Acute Myocardial Infarction
BMSC	Bone Marrow Stem Cell
CCS	Canadian Cardiovascular Society Angina Scale
CDC	Center for Disease Control
COMET	Core Outcome Measures in Effectiveness Trials
IP	Intellectual Property
MLHF	Minnesota Living with Heart Failure
NGT	Nominal Group Technique
NYHA	New York Heart Association
OMERACT	Outcome Measures in Rheumatology
QOL	Quality of Life
SF-36	Short Form-36

CHAPTER 1: INTRODUCTION

Background

Establishing standardized Quality of Life (QOL) core outcomes in stem cell clinical trials is important to ensure that (1) researchers and clinicians can make informed decisions and (2) clinical trials are using the same units and measuring those units in the same way (Clarke, 2007; Thornley & Adams, 1998). Standardization of outcomes is also important according to COMET (Core Outcome Measures in Effectiveness Trials) because such standardization makes "it easier to compare, contrast, and synthesize" clinical trial outcomes, while reducing bias and incongruity (University of Liverpool, 2010). However, before core outcomes in stem cell clinical trials can be established, it is necessary to describe and evaluate the QOL core outcomes currently in use. To date, some research has been conducted in the area of bone marrow stem cell (BMSC) clinical trials as shown in Tables 1 and 2. However, there remains a dearth of standardized QOL core outcome measurements in the area of cardiovascular clinical trials.

Bone Marrow Stem Cells

The history of BMSC transplants dates back to 1939 when Osgood, Riddle, and Mathews (1939) unsuccessfully transfused BMSC to a patient with aplastic anemia. In 1940, a patient purportedly recovered from aplastic anemia after Morrison and Samwick (1940) injected BMSC from several compatible donors. Mathé, a stem cell pioneer, performed the first BMSC transplants on six physicists exposed to radiation from a nuclear site accident in Yugoslavia in 1959 (Martin, 2010). Four years later, Mathé proclaimed BMSC transplantation as a cure for leukemia, and today BMSC transplantation is used as a treatment modality in certain types of cancers. Nearly 50

years later, Strauer et al. (2002) published one of the first stem cell cardiovascular studies. Their research demonstrated that BMSC was safe and effective for intracoronary transplantation and could be associated with myocardial regeneration and neovascularization (Strauer et al. 2002).

Currently, organ transplant demand far surpasses supply with a growing number of heart failure cases that require transplantation. From 1995 to 2011, there were 250,000 candidates age 50-64 years ("baby boomers") awaiting transplantation according to Organ Procurement and Transplant Network (2011). The United Network for Organ Sharing (2011) reported that currently there are 111,562 wait list candidates. As of March 2011, only 6,709 received organ transplants from 3,346 donors. In 2008, the American Heart Association (AHA) (2011a) reported 2,163 heart transplants, which is a decrease from the previous year of 2,210 cases in 2007. Such cases underscore the demands for innovative cardiovascular disease BMSC treatments. Today, approximately 9,500 BMSC transplants are performed annually at more than 200 international treatment centers, and the longest post-transplant survival period is 20 years (Thomas 1990).

Bone Marrow Stem Cells to Treat Cardiovascular Disease

BMSC treatment offers new hope as an alternative therapy to restore cardiac structure and vascularity in patients with non-ischemic or ischemic heart failure (Silva et al. 2004). Cardiac stem cell therapy may regenerate the myocardium by creating new heart muscle (cardiomyogenesis) or creating new pathways or vessels (angiogenesis). Of the 14 major clinical trials cited by Wei et al. (2009), the results remain inconclusive due to several factors (i.e., delivery technique, optimal dosage, best cell types, and low transdifferentiation). Additionally, none of these studies included any QOL assessments.

Quality of Life

The World Health Organization (1948a) recognized: "Health is a state of complete physical, mental, and social well-being—not merely the absence of disease, or infirmity." According to Testa and Simonso (1996), in 1973, a MEDLINE database search on "quality of life" listed only five articles; during "subsequent five-year periods, there were 195, 273, 490, and 1252 such articles." Twenty years ago, clinicians were skeptical of QOL measures, which were considered subjective and soft (Shipper, 1983):

> The scientists may use rating scales and visual analogue scales to measure pain (not the pain as such but what patients say about their pain), and they may even invent scoring systems quantifying types of handicaps; but when they talk about measuring quality of life they have gone too far. (Wulff, 1999)

QOL has been defined as a perception about one's physical and mental health over a specific time, which is dependent on one's values, goals, expectations, standards, and concerns (CDC, 2010a; WHO, 1997b; JAMA, 2002). QOL is complex system in which extrinsic life-changing factors can affect one's physical health and psychological state. Muldoon et al. (1998) identified two operational characteristics of quality of life—"objective functioning and subjective well-being." These characteristics measure the impact of illness and treatment relative to daily life activities and satisfaction. Objective functioning measures the patient's physical well-being and functional ability, whereas subjective well-being measures emotional and social well-being (Cella, 1994).

QOL is an important component of treatment efficacy. Some patients believe that QOL is more important than length of life, as a recent study funded by the European Commission

indicated. The PRIMSA group and Kings College London conducted a telephone survey of 9,344 respondents. The study addressed European respondents' preference for QOL versus quantity of life from seven countries: England, Belgium, Germany, Italy, the Netherlands, Spain, and Portugal. The survey asked respondents about their priorities when faced with a life-threatening disease with limited time to live: 71% wanted to improve QOL, whereas only 4% thought both QOL and health were equally important (BMJ Blogs, 2011a; King College London, 2011).

Historically, empirical evidence was used to determine survival; however, according to Nicolau (cited in Shipper, 1983), "quality of life is a critical factor in determining survival." Patients want to know the benefits of the treatment regardless of its scientific value. Alternatively, some patients may opt to decline treatment due to the poor QOL caused by the treatment itself.

Patient satisfaction has a direct impact on QOL, and research has confirmed that patients with better QOL live longer (Fox Chase Cancer Center, 2007). Stressors, disease impact, and treatment efficacy may negatively affect QOL outcomes. Alternatively, optimism and social support may positively affect QOL outcomes; such an effect is known as the response shift model wherein patients' internal standards, values, treatment, or a change in health status occur (Ring et al., 2005; Beeken, Eiser, & Dalley, 2010).

QOL measurement in evidence-based medicine supports decision-making, resource allocation, healthcare policy, prognostic indication, and determining interventions (Donald, 2003). Such measurement is essential to determine whether treatment is efficacious or detrimental to a patient's QOL. QOL can be measured through validated questionnaires or semi-structured interviews to evaluate patients physical, functional, social, and emotional well-being. According to PROMIS (2011), at least 106 generic instruments have been used to assess an

expansive collection of health domains specific to an array of health conditions and diseases. In contrast, PROMIS (2011) indicated that there are only 35 cardiovascular disease disease-specific instruments.

Core Outcomes

Minimum standards are established by core outcome sets, which are assessed and documented in all health related clinical trials (University of Liverpool, 2010). Developing core outcomes in clinical trials is important for three reasons. First, core outcomes produce homogenous trials for a methodological review, whereas the analysis of heterogeneous trials may produce inconsistent results. Second, core outcomes prioritize points-of-view important to patients and clinicians, whereas non-core outcomes-based research may focus on outcomes most significant to the researcher's viewpoint. Third, core outcomes may eliminate bias by reporting specific results that are both positive and negative, whereas many trials only report positive results (Sinha, Smyth, & Williamson 2011).

Core outcomes development requires a combined consensus from authoritative specialists and patient groups. Sinha, Smyth, and Williamson (2011) discussed the dearth of guidance in core outcome development. However, the Delphi technique, which can help minimize conformity through peer pressure and dominant individuals (Dalkey, 1968), also can be used to develop core outcomes, according to Outcome Measures in Rheumatology (OMERACT) collaborators (Sinha, Smyth, & Williamson, 2011).

Additional informal and formal consensus techniques include Nominal Group Technique (NGT) and the National Institute of Health Consensus Development Conference (Murphy et al. 1998). Upon reaching consensus, the next step is to identify potential instruments to measure core outcome sets, which are reviewed for feasibility, validity, and responsiveness (Sinha, Smyth, & Williamson, 2011). One initiative that provides reporting standards guidance and the development of core outcome sets for use in therapeutic clinical practices is known as Core Outcome Measures for Effectiveness Trials (COMET).

COMET Initiative

The COMET Initiative promotes the establishment and utilization of core outcomes through the collaboration of scientific investigators and institutions (BMJ Blogs, 2010b). COMET specifically focuses on certain variables and how they are measured in response to the effects of illnesses on patients. To date, the COMET Initiative has developed core outcome sets in over 40 therapeutic areas such as cancer, rheumatology, chronic pain, and maternity care (University of Liverpool, 2010). The use of COMET's core outcome sets may enable a standardization that will allow clinicians to analyze whether QOL core outcomes have improved or declined from study to study. By standardizing QOL core outcomes, a comparative baseline can be provided with which to analyze treatment efficacy. If standardization is not developed, patients will continue to be recruited into stem cell clinical trials with no minimum standards for QOL core outcomes. As long as there are no standards, this problem of heterogeneous clinical trials will persist.

Purpose of the Study

This study addressed the research question: *What are the QOL core outcomes currently being measured in stem cell clinical trials?* The aim of this study was to describe and evaluate the quality of life core outcomes currently being measured in US and European stem cell clinical trials.

The study's objectives were to:

1. Describe the timing/frequency intervals, and methodology of QOL core outcomes being measured in bone marrow stem cell clinical trials.
2. Describe the timing/frequency intervals, and methodology of QOL core outcomes being measured in cardiovascular stem cell clinical trials.
3. Compare and contrast QOL core outcomes measured in both groups (bone marrow and cardiovascular stem cell clinical trials).
4. Assess patient satisfaction with the QOL outcomes that currently are measured in cardiovascular stem cell clinical trials.
5. Explore possible standardization of QOL core outcomes in cardiovascular stem cell clinical.

Summary

The impact of the COMET Initiative may change the way clinical trials are conducted; in other words, investigators may be able to evaluate homogeneous stem cell clinical trials with a consistent baseline. The need for research on QOL core outcomes is clear. When clinical trials lack standardized QOL core outcomes, this omission may undermine the clinical trials' efficacy,

whereas research results on QOL core outcomes may influence how clinical studies are developed and used in the future. Furthermore, using the COMET Initiative as a guide, this study will evaluate the potential for using standardized core outcomes in cardiovascular BMSC clinical trials. Effectively standardized QOL core outcomes in stem cell clinical trials may produce significant treatment benefits to millions of aging people in a currently overburdened health care system.

CHAPTER 2: LITERATURE REVIEW

Heart failure is on the rise due to the increasing age of the United States' population. Additionally, the Center for Disease Control (CDC) estimated that it would "cost the United States $316.4 billion (health care services, medications, and lost productivity) in 2010" (CDC, 2010b). Similarly, in Europe, cardiovascular disease is the most deadly disease among both sexes and causes as many as half of all deaths annually (around 2 million). According to the European Heart Network (2009), cardiovascular disease costs approximately €192 billion annually. Accordingly, heart failure treatments have become increasingly important due to the high number of cases (Perin et al. 2003a) and the economic burden of those cases (Bundkirchen & Schwinger, 2004). Of the 2,426,264 deaths reported in the United States in 2006; 631,636 died of heart disease, which accounted for 26% of deaths (Heron et al., 2009; CDC, 2010b). According to Perin et al. (2003a), "no-option" heart failure patients are subjected to aggressive therapeutic interventions with "a potential yearly mortality rate as high as 50%, and for these patients, therapeutic options remain limited." Current studies suggest that BMSC treatments may offer a cost effective alternative treatment to heart failure patients.

QOL in Bone Marrow Stem Cell Research Trials

The 1990 National Cancer Institute clinical trial and QOL expert workshop addressed QOL end-point implementation (Nayfield et al. 1992). The workshop concluded that the selection of QOL core instruments should be based on the following criteria: (1) general and disease specific evaluation and (2) reliable, valid, and psychometric evaluation. The group also recommended

specific timing intervals for follow-up: (1) baseline (prior to randomization), (2) pre-treatment, (3) during treatment, (4) completion or discontinuation of study, and (5) completion of study (Nayfield et al. 1992). Table 1 shows that the majority of the trials conducted between 1991−1993 did not include the 1990 workshop group recommendation, as discussed above.

Table 1 adapted from Ca ncer BMSC Trials (Andrykowski et a l., 1995; Hjermstad & Kaasa, 1995)

	Outcomes Measure Assessment	
Author's Name	**Follow up (months)**	**QOL Instrument**
Achard & Zittoun (1992)	Before BMT, day 1,11, and 2 1 post-treatment	Modified EORTC-QLQ C30, HAD
Aeschelmann et al.(1992)	7-96 mo post-BMT	Interview, modified CJDM
Altmaier et al. (1991)	25-41 mo post-BMT	Phone interview on health, functioning
Andrykowski et al. (1989)	3-52 mo post-BMT	POMS, FLIC
Andrykowski et al. (1989)	3 times post-BMT	POMS, FLIC, SIP
Andrykowski et al. (1990)	12-96 mo post-BMT	POMS, PAIS, SIP
Adrykowski et al. (1990)	Minimum 1 year post-BMT	POMS, FLIC, SIP, PAIS
Baker et al. (1991)	6-149 mo post-BMT	Role checklist, SLDS, CSAL, POMS, BPNAS
Baruch et al. (1991)	Minimum 6 mo post-BMT	HAD, questionnaire on health, sexual function
Belec (1992)	12-38 mo post-BMT	Interview, QLI-Cancer, checklist
Chao et al. (1992)	1 year follow-up, every 3 mo, from day + 90	Phone interview
Claisse et al. (1992)	BMT performed from 1984-1989	Questionnaire with 30 selected items
Collins et al. (1989)	Days 3,7, 12 and 19 of isolation	Semi-structured interviews

Colon et al. (1991)	Review ratings of charts prior to BMT	Psychiatric history, obtained DSM III, support
Curbow et al. (1993)	6-149 mo post-BMT	Role checklist, SLDS , CSAL, POMS, BPNAS
Cust et al. (1989)	Minimum 6 mo post- BMT	Interview, designed questionnaire
Decker et al. (1989)	One week pre-BMT, 1,6.5, 12 mo post-BMT	Exercise testing, BDI
Dermatis & Lesko (1991)	Within 48 hours after admission	Questionnaire, BSI, Ways of coping list
Ersek	Pre-BMT, days 9-12, and 25-28 post-BMT	In-depth qualitative interviews
Ferrell et al. (1991)	Minimum 100 days post-BMT	BMT-QQLS as an in depth interview
Ferro et al. (1992)	Minimum 6 mo post-BMT	Interview on psychosocial functioning
Futterman et al. (1991)	Review ratings of pre-BMT charts	Psychiatric history, social support, coping
Gaston-Johansson et al. (1992)	2 days pre-BMT, 5, 10, and 20 days post-BMT	PoM, STAI, BDI, MHLC, CSQ
Grant et al. (1992)	Minimum 100 days post-BMT	QOL-BMT questionnaire
Hengeveld et al. (1988)	12-60 mo post-BMT	Interview, BDI, SCL-90
Jenkins et al. (1991)	After discharge from BMT unit	Interview, HAD, PAIS,EPQ, CIDL
Kennedy et al. (1990)	13-62 mo post-BMT (median 30)	Phone interview, semi structured
King (1988)	At time of admission and discharge	NSSQ, BDI
Larson et al. (1993)	Day 1 post-BMT, days 7-10,20-23,3O-34	SDS, POMS
Lesko et al. (1992)	Minimum 5 years from end of treatment	BSI, MHI, IES, SAS,ABCL, DSFI, cohesion
Magid et al.(1988)	Baseline pre-BMT, 1 mo post-discharge	POMS, FLIC
Mashberg (1989)	Minimum 1 year post-BMT	BSI, DAQ, IES, PAIS,DSFI
McElwain et al. (1989)	6 mo-3 years	Infection rates, pain
Mumma et al. (1992)	Minimum 1 year post-BMT (mean 47 and 64)	Interview, BSI, POMS, DAQ, IES, PAIS, DSFI

Peters et al. (1993)	Minimum 1 year post-BMT (median 2 years)	Phone interviews, FLIC, SDS
Rodrigue et al.(1993)	Pre-BMT (mean 23 days)	BDI, STAI, STAXI,MCMQ, MMPI
Schmidt et al. (1989)	Every 3 mo, 3-140 mo (median 3.6 years)	Specifically designed questionnaire
Schmidt et al. (1993)	Minimum 12 mo post-BMT	Phone or personal interviews
Smith et al. (1984)	Pre-or post-BMT, most in the peritranspl. period	Personal interview, SRE data
Steeves (1992)	Pre-BMT to day 100	Hermeneutic methods, observation, interaction
Syrjala et al. (1990)	Pre-BMT and 1 year post-BMT	SIP, BDI, BES, coping style
Syrjala et al. (1993)	Pre-BMT, 90 days and 1 year post-BMT	SIP, BSI, BDI, family cohesion, coping style
Vose et al. (1991)	13-62 mo post-BMT	Phone interview on appearance, adjustment
Winer et al. (1992)	Min. 1 year post- BMT	FLIC, SDS, PAIS, phone interview
Wingard et al. (1992)	6-149 mo post-BMT (median 47)	MOS, SLDS, CSAL
Wingard et al. (1991)	6-149 mo post-BMT	Mailed survey, health perception scale
Wolcott et al. (1986)	Min 1 year post-BMT	SAS, POMS, Simmons
Zabora et al. (1990)	Pre BMT, 6-48 mo post BMT	SI, ICC, SLDS

Table 1 adapted from (Andrykowski et al., 1995; Hjermstad and Kaasa 1995) Cancer BMSC Trials

Furthermore, Hjermstad and Kaasa (1995) reviewed 57 BMSC trials showing that only 11 incorporated a baseline assessment of QOL. Andrykowski et al. (1995) conducted one of the largest multicenter QOL BMSC trials of its time and used instruments specially designed for assessing post-BMSC QOL. However, one of the study's limitations was that QOL assessments

were not validated for BMSC patients. It seems curious that such a large study would use non-validated instruments and therefore would be subject to ambiguous interpretation.

QOL assessment is fundamentally important throughout the entire life cycle of the BMSC process. Without QOL assessment, patients cannot give true informed consent, nor can they be fully aware of the full continuum of treatment outcomes. Additionally, QOL assessments augment the clinical decision-making process for the clinician and the patient (Hjermstad & Kaasa, 1995). Moreover, QOL assessments are the most consistent prognostic factors for post-transplant psychosocial problems. Consequently, pre-transplant QOL assessments identify these issues and enable clinicians to initiate intervention programs (Hjermstad & Kaasa, 1995).

However, it is not clear why the guidelines of the 1990 workshop were not fully realized or implemented in various studies. Clinical trials without QOL assessments create disparity due to ambiguous results. This inconsistency renders clinicians and patients unable to make informed decisions, as the full continuum of treatment options is not available for analysis.

QOL in Bone Marrow Stem Cell Cardiovascular Research Trials

Treating cardiovascular disease with BMSC is a novel approach that began to emerge in 2002. Perin et al. (2011b) conducted a study, which included QOL for cardiovascular BMSC. Two questionnaires were administered: (1) general Short Form-36 (SF-36) and (2) disease specific Minnesota Living with Heart Failure (MLHF). Findings included significant improvement when compared to baseline, whereas, patients in the control group showed no marked improvement over baseline (Perin et al. 2011b). This is a significant study because they include baseline measure as compared to prior studies. BMSC treatment potentially can be cost effective as noted by Mathur

and Martin (2004); however; one problem is there is no intellectual property (IP) associated with autologous BMSC (Hughes, 2004). Large-scale trials would be prohibitive due to lack of funding, which is why cellular processing methods, culture medium, delivery techniques, and catheter types can vary greatly in each trial (Hughes, 2004). For this reason, many off shore clinics have emerged to take advantage of the lack of IP. The only way to educate desperate participants is to have standards.

Wei et al. (2009) cited several major clinical studies, which used BMSC in treating acute myocardial infarction (AMI). However, several interesting factors (i.e., delivery technique, optimal dosage, best cell types, and low transdifferentiation) further illustrate the inconsistency in clinical trial methodology. Interestingly, none of the aforementioned studies cited by Wei et al. (2009) included any QOL assessments.

Several 2002-2011 cardiovascular BMSC clinical studies revealed problems with QOL, such as inconsistent QOL assessment and irregularities in timing/frequency of follow-up with patients. Furthermore, the studies had other flaws, such as treatment timing, delivery techniques, optimal dosage, and the best cell types. For example, the best time to treat acute myocardial infarct (AMI) with BMSC is between 5-14 days. This timing is based upon two factors: (1) five days after an AMI the inflammation process is the most intense and for this reason, BMSC is not recommended; and (2) scar tissue formation occurs 14 days post AMI (Yousef et al. 2009). Table 2 shows that AMI studies tend to administer the stem cells at different times. Time of administration may affect treatment efficacy and QOL; however, these outcomes cannot be determined because they are not measured.

Table 2: AMI Transplant Days in BMSC Trials

Study Name	Study Type	Transplant (Days)
ASTAMI (Norway) Lunde et al. 2005	AMI	5-9 d
BALANCE (Germany) Yousef et al. (2009)	AMI	7 ± 2 d
BOOST (Germany) Wollert et al. 2004	AMI	5d
BONAMI (France) Roncalli et al. 2010	AMI	7–10 d
REPAIR-AMI (Germany) Schächinger et al. 2006	AMI	3 – 7 d
Strauer et al. 2002 (Germany)	AMI	5-9 d
TOPCARE-AMI (Germany) Assmus et al. 2002	AMI	4.3±1.5 d

Delivery techniques varied from study to study. For example, Lunde et al. (2005) and Yousef et al. (2009) used angioplasty balloon catheter to deliver BMSC; however, Yousef et al. (2009) used twice the number of stem cells and a different delivery technique. One could argue plausibly that some patients experienced the same benefits from angioplasty with or without BMSC. Perhaps some patients obtained benefit solely from angioplasty, which restores blood flow, as opposed to receiving benefits strictly from BMSC treatments. BMSC trials draw disparate amounts of bone marrow, and determination of optimal dosage is not yet established (Lunde et al., 2005; Schächinger et al., 2006; Perin et al., 2003a; Roncalli et al., 2010; Patel et al., 2005; and