It is on my skin, on my soul, and on my life.

Development of a disease-specific quality of life instrument for adult patients with acute cutaneous leishmaniasis in Iran

Alireza Khatami
Dedication

This thesis is dedicate to my dear mother:

Parvin Mortazavi Nejad

who is my everything.

In memory of my dear father:

Ali Akbar Khatami

(1940-2011)
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Abstract

Background: Cutaneous leishmaniasis (CL), is the most common form of a group of diseases known as leishmaniasis. They are caused by obligatory intracellular protozoa from the genus *Leishmania* and transmitted by sandflies. Over 350 million people are at risk of getting leishmaniasis and 1,000,000 to 1,200,000 individual get CL each year, the majority of them are living in developing countries. CL may affect a patient’s physical and mental health, and social relations impairing his/her quality of life (QoL).

Aim: The aim of this thesis was to develop a disease-specific instrument for measuring QoL in adult patients suffering from the acute form of CL in Iran according to a needs-based approach.

Methods: This thesis used a mixed-method approach and was based on two quantitative studies and one qualitative study. The first study was a systematic review on the randomized controlled clinical trials (RCTs) conducted on acute CL in the Old World. The second one was a qualitative content analysis study conducted through interviews with patients with CL in Iran. The third study was a psychometric evaluation of an instrument that was developed according to the results of the second study. For making a QoL instrument with fundamental measurement properties, the Rasch method was used.

Results: The findings of the first paper demonstrated that the majority of the 50 reviewed RCTs were of poor quality of conduct and report. An important finding was that none of those studies included a patient-reported outcome in their primary, secondary, or even tertiary outcome assessments. To obtain the patients’ lived experience and perspectives on their disease, 12 individual in-depth interviews were conducted with patients with CL. Four themes were developed: "Fearing an agonizing disease" reflects patients' experiences of disease development resulting in sadness and depression, "struggling to cope" and "taking on the blame" both illustrate how patients experience living with the disease, which included both felt and enacted stigma as major social concerns. "Longing for being seen and heard" refers to patients' experiences with healthcare as well as their expectations and demands from communities and healthcare system to be involved in closing the knowledge and awareness gap. The third study was conducted as a survey on 107 patients with acute CL answering 50 questions with four response categories focusing different aspects of QoL, named "P-CL-QoL", an acronym for Preliminary Cutaneous Leishmaniasis Quality of Life instrument. The Rasch fitness criteria for the original 50-item questionnaire indicated that it was not optimal for fundamental measurement of the QoL in CL patients. Two more Rasch models were developed by merging the last two response categories and making a 3-point Likert scale, and the three last response categories, making a dichotomized “Yes” and “No” response choices to each item. The final 34-item instrument with dichotomous responses showed improved measurement properties including very good targeting and item-separation index, internal consistency (Chronbach’s α=0.94), and a log-likelihood Chi square=2242.50 (degree of freedom=2640, and \( P=1.000 \)) indicating excellent fitting to a Rasch model. This version was named Cutaneous Leishmaniasis Quality of Life instrument (CL-QoL). According our findings, the mean (±standard deviation) of raw scores and 0-34 scaled measures of the participants were 15.9 (±9.2) and 16.8 (±6.9), respectively. The impact of CL on the QoL of the patients was none to minimal in 17.0 %, mild in 25.0 %, moderate in 31.8 %, high in 12.5 %, and very high in 13.7 % of the participants. QoL impairment was not related to the sex and age of the individuals, geographic location where CL was caught, duration of the disease, and its severity (\( P>0.05 \)).

Conclusion: This thesis demonstrated that there is a lack of patients’ reported outcomes in clinical trials on CL, and that mental and social dimensions of CL are complex and adversely affect patients' lives by causing psychological burden and limiting their social interactions. The health authorities have to plan programs to increase the disease awareness in communities and among healthcare professionals to prevent the existing stigma and improve patients' social condition and medical care. While we could suggest a diseases-specific QoL measurement instrument through our third study, we acknowledge that the developed instrument may not be optimal and has to be validated in other populations, preferably using the Rasch method.

Keywords: cutaneous leishmaniasis, fundamental measurement, needs-based approach, neglected tropical disease, probabilistic model, quality of life, qualitative content analysis, the Rasch model
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACL</td>
<td>Anthroponotic Cutaneous Leishmaniasis</td>
</tr>
<tr>
<td>AOWCL</td>
<td>Acute Old World Cutaneous Leishmaniasis</td>
</tr>
<tr>
<td>CL</td>
<td>Cutaneous Leishmaniasis</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRTSDL</td>
<td>Center for Research and Training in Skin Diseases and Leprosy</td>
</tr>
<tr>
<td>DCL</td>
<td>Diffuse Cutaneous Leishmaniasis</td>
</tr>
<tr>
<td>DIF</td>
<td>Differential Item Functioning</td>
</tr>
<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index</td>
</tr>
<tr>
<td>DSQL</td>
<td>Dermatology Specific Quality of Life</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>European Quality of Life-5 Dimension</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>LCL</td>
<td>Localized Cutaneous Leishmaniasis</td>
</tr>
<tr>
<td>MCL</td>
<td>Mucocutaneous Leishmaniasis</td>
</tr>
<tr>
<td>MnSq</td>
<td>Mean Square</td>
</tr>
<tr>
<td>MOS</td>
<td>Medical Outcome Study</td>
</tr>
<tr>
<td>PCAR</td>
<td>Principal Component Analysis of Residues</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient-Reported Outcome</td>
</tr>
<tr>
<td>PSORIQoL</td>
<td>Psoriasis Index of Quality of Life</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>QoLIAD</td>
<td>Quality of Life Index for Atopic Dermatitis</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RSM</td>
<td>Rating Scale Model</td>
</tr>
<tr>
<td>SF-36</td>
<td>36-item Short Form</td>
</tr>
<tr>
<td>SIP</td>
<td>Sickness Impact Profile</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VL</td>
<td>Visceral Leishmaniasis</td>
</tr>
<tr>
<td>ZCL</td>
<td>Zoonotic Cutaneous Leishmaniasis</td>
</tr>
</tbody>
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List of Original Papers

This thesis is based on the following papers


Papers I and II are reprinted in the thesis with permission of the publishers.
1. Introduction

This thesis is focused on the quality of life (QoL) of adult patients who suffer from cutaneous leishmaniasis (CL) in Iran. CL is a form of a group of diseases named leishmaniases. Leishmaniases are caused by an obligatory intracellular protozoon from the genus *Leishmania*. Clinical forms of Leishmaniases are diverse. On one side, there is localized CL (LCL) which manifests with self-limiting skin lesions. On the other side, a form of leishmaniasis known as visceral leishmaniasis (VL) or kala-azar exists. VL is a severe systemic disease which if not be treated properly is fatal.

While anthropogenic CL (ACL) in which the disease can be transmitted from a human being to another one is well-known, most cases of CL and other forms leishmaniases are considered as zoonotic diseases because of having animal reservoirs. Zoonotic CL is abbreviated as ZCL.

For transmission of *leishmaniasis* to humans four factors must exist: a) the human being, b) the reservoir (can be a human being in ACL), c) the vector which belongs to a group of insects commonly known as sandflies, and d) the protozoa. *Leishmaniasis* is a tropical disease. It is because both the reservoirs and the vectors exist in the tropic and subtropics. *Leishmaniasis* is considered one of the neglected tropical diseases (NTDs) by the World Health Organization (WHO) affecting more than one billion individuals and cost billions of dollars in poor countries around the world.

Living in Iran, where CL is endemic, I was quite familiar with the impact of the CL on the lives of the patients who got it. After my graduation as a dermatologist in 2002 and working as a fulltime faculty member at a referral center for patients with CL as well as travelling extensively to the areas where CL is endemic, I noticed that there was no patient-reported outcome (PRO) in the assessment of the patient’s outcomes in the research studies conducted on CL. My personal experience was supported by the findings of a systemic review that I conducted on the randomized controlled clinical trials (RCTs) of CL later and is included in this thesis (Paper I). This paper indicated that none of the 50 RCTs that were eligible for being included in this review used a PRO measure such as QoL. This paper also provides a background on the disease in general and the existing treatments, in particular, with detailed description of the conducted RCTs.

Considering the fact that in many CL cases, physicians and patients, percepts the process of the healing and improvement of the lesions, and the outcome of treatment of the disease differently, motivated me to try to know more about the CL patients’ lived experience which was done through conducting a qualitative content analysis research study as part of this thesis (Paper II).

In addition, CL has some major differences with other dermatologic diseases and conditions for which quality of life instruments were developed. So, the next step was to suggest a disease-specific instrument for measuring QoL in patients with CL. The process
of psychometric evaluation of this instrument has been described in the quantitative study of this thesis (Paper III). Because of its suitability for investigating psychometric properties of QoL instruments, Rasch analysis was used as the main method to investigate the appropriateness of the developed instrument.

This thesis aims to get the CL patients perspective, incorporates it into a PRO like QoL through development of a disease-specific QoL instrument. For this purpose, after providing some background information on the CL and QoL measurement in dermatology, the rationale and objectives of this thesis are stated. Those sections are followed by description of the used methods in each study. The findings are provided. Interpretation and discussions of the findings including the limitations of the studies follow.
2. Background

2.1. Leishmaniasis: Overview and Classification

Leishmaniases are a group of diseases caused by several species of the genus *Leishmania*, a protozoa transmitted by the bite of a tiny insect vector, sandfly. Infections in wild animals usually are not pathogenic, with the exception of dogs, which may be severely affected [1].

The major clinical patterns of the disease in the human host are: cutaneous *leishmaniasis* (CL), which itself can be sub-classified as either localized CL (LCL) or diffuse cutaneous leishmaniasis (DCL); mucocutaneous *leishmaniasis* (MCL), and *visceral leishmaniasis* (VL) [1]. Traditionally, CL has been divided into Old World and New World. Old World CL is found in Asia, Africa, and southern Europe. New World CL is found in Mexico, Central America, South America and occasionally, in Texas and Oklahoma states of the USA [2]. A simple practical classification of different types of leishmaniases in human is demonstrated in Figure 1.

![Figure 1. Simple practical classification of different types of leishmaniases (Courtesy of Dr. Alireza Khatami).](image-url)
2.2. Epidemiology

2.2.1. Global Aspect

CL occurs in Asia, southeast Europe and Latin America [3]. With the exception of Australia and Antarctica, the parasites have been identified throughout the world [2].

The more than 12 million people are living with leishmaniasis, 350 million people in 98 countries, most of which are developing poor ones, are at risk. Annually, more than 2 million new cases of leishmaniasis happens, of which 1.5 million cases are CL, accounted for about 75% of all new cases of leishmaniasis. The majority of all CL cases occurs in 10 countries: Afghanistan, Algeria, Brazil, Colombia, Iran, Iraq, Pakistan, Peru, Syria, and Tunisia. It is considered as a major health problem in 14 countries [3-8]. Figure 2 shows the global distribution of CL [9].

![Map showing the global distribution of cutaneous leishmaniasis](image)

**Figure 2.** Endemic areas for cutaneous leishmaniasis in the world: WHO, 2015 [9]

Bailey and Lockwood noted that epidemics might occur when large numbers of non-immune humans become exposed to infection for the first time. This may occur because of human migration or that of the reservoir hosts. Also, travels from non-endemic areas to endemic areas during activities like wars, military exercises, civilian works, and tourism may result in outbreak of the disease in certain populations [3].

Oryan and Akbari described climate and environmental changes such as alterations in temperature and water storage, irrigation habits, deforestation; immunosuppression caused by HIV or organ transplant; development of drug resistance because of extensive use of anti-leishmania drugs in veterinary, increased traveling to endemic areas, and dog importation as the worldwide risk factors for spread of leishmaniasis [10]. They also considered armed conflicts and poverty as major contributors to the spread of this group of diseases.
Through using different data sources and applying various models, climate change has been investigated as a contributing factor to the extension of the distribution of leishmaniases, which has been basically done by estimating the distribution of the vectors under different scenarios of global warming [11, 12]. While the scope of this topic is beyond this text, it is interesting that based on whether a small area vs. continental scale was investigated, the results could be different. For example, Purse et al. stated that according to their models, the effect of the global warming in the south- and meso-America continent predicted a contraction of New World CL by 35% to 50% [12] by 2050, while some localized studies such as a study in Andean Colombia by Pérez-Flórez et al. indicated that an increase in temperature was associated with an increase in CL incidence [13]. Other environmental factors that can play a role in the distribution of CL are urbanization and deforesting [11-13]. Natural disasters can change CL incidence dramatically. After a major earthquake in December 2003, incidence of CL in Bam increased from about 1.9/1000 in 2003 to more than 7.6/1000 in 2005 [14]. The observed surge in the number of CL cases in the following months of the disastrous earthquake caused by destruction of about 90% of the city’s infrastructure including its homes, roads, electricity, water pipelines, and health facilities like health posts, which resulted in more exposure to sandfly bites [14].

Berry and Berrang-Ford showed a significant relationship of CL and areas where conflicts and/or political terror level is very high (odds ratio [OR]=2.38, 95% Confidence Interval [95% CI]: 1.40-4.05). [15].

Eid et al. investigated the risk factors for CL in two communities in Bolivia in a cross-sectional study [16]. They concluded that after adjusting ORs in their multivariate analysis, the only risk factor for CL was male sex (OR=3.2, 95% CI: 1.6-6.6) which has been explained by more exposure of males to the outdoors and consequently to more sandfly bites because of their works such as forestry and mining, as well as their leisure activities like hunting and fishing [16].

2.2.2. Epidemiology of CL in Iran

Iran is endemic for CL. Almost all CL cases are caused by either L. tropica or L. major. CL has been reported from all provinces and is endemic in many of them. In 2012, a total number of 20,947 cases were registered in Iran and the incidence rate was 27.2/100,000 persons [17]. The highest reported incidence rates in 2012 were reported from Ilam, Fars, and Khorasan Razavi provinces at 98.7, 86.8, and 81.9/100,000 persons. Around 56.6% of recorded CL cases were male and the highest incidence rates were observed in children 1 to 9 years old [17]. In some villages surrounding Kashan, cumulative incidence of CL was estimated to be around 13.1% in 1996 [18]. A recent study showed an incidence rate of 47/100,000 inhabitants in the city of Kashan in 2016 [19].

Distribution of CL in Iran is demonstrated in Figure 3.
2.3. Etiology

The causative agents of CL in the Old World are: *L. major*, *L. tropica*, *L. aethiopica*, and rarely *L. infantum*. For most species of *Leishmania*, an animal reservoir is required for endemic conditions to persist. Common hosts in Old World are domestic and feral dogs, rodents, foxes, jackals, wolves, raccoon-dogs and hyraxes. Most commonly observed Old World vectors are sandflies belonging to the genus *Phlebotomus* and include: *Ph. sergenti* and *Ph. papatasi* for transmission of *L. tropica* and *L. major*, respectively. Humans are generally considered as accidental hosts [2, 20]. Life cycle of *Leishmania* is summarized in Fact Box 1.

2.4. Clinical Manifestations

Old World and New World CL are quite different in their epidemiology, causative parasites, vectors, reservoirs as well as the clinical presentation, treatment indications, and prognosis, so it looks reasonable to consider them as different diseases [4]. Since other types of leishmaniasis are irrelevant to this study and almost all cases of CL that occur in Iran are caused by *L. major* or *L. tropica*, herein, only clinical manifestations of Old World CL due to *L. major* and *L. tropica* are discussed.

Clinically, acute Old World CL (AOWCL) is seen in two forms: anthroponotic cutaneous leishmaniasis (ACL) and zoonotic cutaneous leishmaniasis (ZCL). ACL is also known as dry, urban or late ulcerative form and is generally attributed to *L. tropica*. Other names for the ZCL form which is caused by *L. major* are wet, rural, or early ulcerative form. In human, the initial sign of infection is the appearance of an erythematous papule or nodule at the feeding site of the female sandfly. It appears within 1 week to 3 months after sandfly bite. In a typical ZCL infection, the primary lesion usually develops into an ulcer with a violaceous border which heals spontaneously in several weeks to months, resulting in a scar (Figures 4-8). Ulceration is not a characteristic feature of ACL lesions. Due to
presence of a thick adherent scale on the lesion, hyperkeratosis is the dominant feature of ACL lesions [1, 20-22].

**Fact Box 1. Life cycle of *Leishmania.***

*Leishmania* has two forms in its life cycle, promastigote and amastigote. The amastigotes transform to promastigotes in the gut of the vector, sandflies from the genus *Phlebotomus.*

1. Occultation of the promastigote form of the parasite into the skin of a host occurs when an infected female sandfly bites to take blood.
2. Hosts’ macrophages and some other mononuclear cells phagocytose the promastigotes.
3. Promastigotes transform into amastigote form inside the macrophages.
4. Amastigotes proliferate inside the macrophages and destroy them through rupturing their cell membrane, infecting other cells.
5. When a sandfly takes a blood meal from an infected host, it takes the infected cells which have amastigotes inside them.
6. The infect cells will be ingested in the gut of the sandfly.
7. The protozoa transform from the amastigote form to the promastigote form.
8. The promastigotes divide in the gut of the sandfly and migrate to its proboscis, stuffing it. This sandfly is infected and can infect a host.

Source: Centers for Diseases Control and Prevention (CDC), (Atlanta, Georgia, USA). Life cycle image and contents courtesy of Division of Parasitic Disease ([DPDx]) [23].
Leishmaniasis recidivans is a form of CL that is also known as chronic CL and happens in about 4% of patients with ACL. The clinical presentation consists of development of brown yellow to red papules in or around the scar of an old ACL lesion (Figure 9). The papules may coalesce and resemble a form of skin tuberculosis known as lupus vulgaris. Leishmaniasis recidivans may progress over the years and is difficult to treat [1].

Figure 4. Acute cutaneous leishmaniasis due to *L. major* on the face of a boy. (Courtesy of the Center for Research and Training in Skin Diseases and Leprosy, with permission).

Figure 5. Acute cutaneous leishmaniasis due to *L. major* on the hand of a young man. (Courtesy of the Center for Research and Training in Skin Diseases and Leprosy, with permission).

Figure 6. Acute cutaneous leishmaniasis due to *L. major* on the dorsal foot. (Courtesy of the Center for Research and Training in Skin Diseases and Leprosy, with permission).
Figure 7. Extensive scar formation after infection with *L. major*. (Courtesy of the Center for Research and Training in Skin Diseases and Leprosy, with permission).

Figure 8. Acute cutaneous leishmaniasis caused by *L. tropica* on the nose. (Courtesy of Dr. Ali Khamesipour, with permission).

Figure 9. *Leishmaniasis recidivans* following infection with *L. tropica*. (Courtesy of the Center for Research and Training in Skin Diseases and Leprosy, with permission).
Major differences in clinical course and prognosis of ACL and ZCL are compared in Table 1.

**Table 1.** Major clinical differences between ACL and ZCL [1, 24].

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>AOWCL Type</th>
<th>ACL</th>
<th>ZCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical course</td>
<td></td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Incubation period</td>
<td></td>
<td>Long: 2-8 months</td>
<td>Short: 2 weeks-2 months</td>
</tr>
<tr>
<td>Typical lesions</td>
<td></td>
<td>Dry, hyperkeratotic</td>
<td>Wet, ulcerative</td>
</tr>
<tr>
<td>Number of lesions</td>
<td></td>
<td>1 or 2, usually &lt; 5</td>
<td>Number of the lesions is usually higher in comparison with ACL</td>
</tr>
<tr>
<td>Size of the lesion (largest diameter)</td>
<td></td>
<td>Usually smaller in comparison with ZCL</td>
<td>1-5 cm, may reach 10 cm or more</td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
<td>68 %</td>
<td>Almost 100 %</td>
</tr>
<tr>
<td>Self-healing (12 months)</td>
<td></td>
<td>Long: up to 2 years</td>
<td>Short: usually less than 1 year</td>
</tr>
<tr>
<td>Duration of self-healing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential progression to <em>leishmaniais recidivans</em></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

2.5. Treatment and Prevention

Treatment is indicated in many cases of AOWCL due to *L. major* as well as AOWCL due to *L. tropica* which have to be treated because of the prolonged course of disease, possibility of progression to *leishmaniais recidivans* and the fact that the cases are the reservoirs [2, 24]. Many treatment modalities have been used in the treatment of CL, but pentavalent antimonials are considered as the first line drugs for treatment of CL [25-27]. They have to be administered only as intramuscular, intravenous or intralesional injections and could be associated with severe side effects and significant discomfort [25, 26]. Research for finding more effective, safer, and more cost effective treatments is continued. While interest in conducting experiments and clinical trials using new topical formulations, and on liposomal or nanotechnology-based products has increased in recent years [28-33], some less sophisticated approaches such as using heat therapy has shown more promising results [34]. However, drug resistance to the pentavalent antimonials has been reported and can cause problems in leishmaniases treatment [35-37]. There is no vaccine available for prevention of CL for general human use [38].

2.6. Quality of Life: Overview

The questions of what is the quality of life and how life gains its quality are not new. Throughout the history, many philosophers have tried to find answers for these questions and their different points of views have resulted in considerable controversies. So it is not surprising that nowadays at the beginning of the 21st century, the quality of life is still a matter of debate and there is no specific definition for quality of life (QoL) [39, 40].

Halioua et al. have defined QoL as a broad concept that encompasses important issues such as physical health, psychologic status, level of independence, social relations, and
beliefs [41]. Different approaches to QoL exist and each of them has focused on one or more aspects of QoL.

2.7. Applications of QoL measurement in clinical medicine

Fayers and Machin have discussed different uses of QoL measurement in medicine from their use in either curative or palliative clinical trials, to provide better communication with the patients and understanding their preferences [40]. They have described three broad categories of application of QoL measurement in clinical medicine:

1. As a discriminative measure: which reflects changes of disease burden over time.
2. As an evaluative tool: which is used to measure health status or the impact of a certain disease at a point in time
3. As a predictive measure: which is the use of the instrument for predicting future outcomes for patients.

2.8. Evolution of QoL measurement instruments

It is still under debate how life gets its quality. On one hand, according to the definition by World Health Organization (WHO), health is “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”, the nature of health is multidimensional. [42]. On the other hand, the relation between health status and QoL is not completely clear. These controversies have resulted in different approaches to the QoL. Two major relevant approaches to QoL in AOWCL patients are health-related quality of life (HRQoL) and needs-based QoL [43].

In HRQoL approach, health is central to QoL and its focus is on the individual’s role in society which explains why it is known as a functionalistic approach. The majority of generic QoL instruments such as Sickness Impact Profile (SIP) and Medical Outcome Study (MOS) 36-item Short Form (SF-36) are based on this approach [42].

Needs-based model for QoL was first suggested by Hunt and McKenna in 1992 and has derived from theories of human motivation. Since then, at least 20 disease-specific QoL measurement instruments based on the needs-based approach have been developed. Items in each of these instruments reflect the concerns of the patients rather than those of investigators because the content of each of them was developed directly from interviews with relevant patients [43].

2.9. Types of Quality of Life Instruments

2.9.1. Generic instruments

These instruments are intended for assessing general issues with regard to health irrespective of the disease or condition of the patient. Some of them were initially used to define health and are better called “measures of health status” rather than QoL measurement instruments [40]. The properties of SF-36, SIP and European Quality of Life-5 Dimension (EQ-5D) are demonstrated in Table 2 [40, 44].
Table 2. Properties of SF-36, SIP and EQ-5D.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SF-36</th>
<th>SIP</th>
<th>EQ-5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of development</td>
<td>The SF-36 was developed during the Medical Outcomes Study (MOS) to</td>
<td>To provide a descriptive profile of changes in a person's behavior</td>
<td>To assess health outcome from a wide variety of interventions on a</td>
</tr>
<tr>
<td></td>
<td>measure generic health concepts relevant across age, disease, and</td>
<td>due to sickness</td>
<td>common scale, for purposes of evaluation, allocation and monitoring</td>
</tr>
<tr>
<td></td>
<td>treatment groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Objective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of items</td>
<td>36</td>
<td>136</td>
<td>5 + 1 VAS*</td>
</tr>
<tr>
<td>Population</td>
<td>Adult/adolescent</td>
<td>Adult</td>
<td>&gt; 12 years</td>
</tr>
<tr>
<td>Mode of administration</td>
<td>Computer-administered</td>
<td>Interviewer-administered, self-administered, telephone-administered</td>
<td>Proxy-administered, self-administered</td>
</tr>
<tr>
<td></td>
<td>Interviewer-administered, self-administered, telephone-administered</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time recall</td>
<td>Last month</td>
<td>Today</td>
<td>Today</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Visual analogue scale. †Note: Interviewer-administered by a trained interviewer in person or by telephone
‡Observer, proxy and telephone versions are available on request
2.9.2. Specialty (dermatology)-specific QoL instruments

The vast majority of dermatology practice is out-patient and most of the dermatology patients suffer diseases that are chronic with almost no survival impairment. Consequently, traditional health outcomes like mortality, hospital stay and so on are not relevant to many dermatological diseases [45]. To make more appropriate PRO dermatology-specific QoL Instruments have been developed. These instruments are also known as dermatology-generic QoL instruments. Three well-known dermatology-specific QoLs are:

a. **Dermatology Life Quality Index (DLQI)** [46]

b. **Dermatology Specific Quality of Life (DSQL)** [47]

c. **Skindex** [45, 48]

Characteristics of DLQI, DSQL and Skindex are demonstrated in table 3 [46-48].

2.9.3. Disease (condition)-specific QoL instruments

Due to the wide spectrum of skin diseases in terms of clinical manifestations and diagnostic entities, dermatology-specific QoL tools like DLQI and Skindex cannot be universally used to assess QoL in patients with skin diseases. This has resulted in development of so called disease (condition)-specific QoL instruments in the field of dermatology which out-number the dermatology-generic QoL tools [48]. Just to provide a handful of examples Scalpdex a disease-specific instrument for evaluation of QoL in patients with scalp dermatitis in particular seborrheic dermatitis and psoriasis; DSQL-A and DSQL-CD which are QoL instruments based on DSQL with one and two extra items to evaluate QoL in patients with acne and contact dermatitis, respectively; and a modified DLQI instrument for measurement of QoL in patients with lymphatic filariasis can be listed [45-50].

2.10. Quality of Life in Dermatology

A review of dermatology-specific QoL instruments and disease-specific QoL instruments in dermatology reveals that they usually assess 3 to 8 constructs in order to evaluate patients QoL [44, 46-49]. Chren et al., considered 4 main constructs, physical, emotional, social and cognitive in Skindex. They subdivided physical construct to 2 sub-constructs: limitation and discomfort, and emotional construct to 4 sub-constructs: depression, fear, embarrassment and anger. Taking into account all the sub-constructs Skindex has 8 constructs [45]. Anderson and Rajagopalan reported 5 constructs: physical, social, activities of daily life, work and self-perception in DSQL [39]. During development of disease-specific QoL instrument, Chen et al. detected 3 constructs: physical, emotional and social in Scalpdex [49].
### Table 3. Characteristics of DLQI, DSQL and Skindex.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DLQI</th>
<th>DSQL</th>
<th>Skindex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Developed by</strong></td>
<td>Finlay AY</td>
<td>Anderson RT and Rajagopalan R</td>
<td>Chren MM et al</td>
</tr>
<tr>
<td><strong>Year of development</strong></td>
<td>1994</td>
<td>1997</td>
<td>1996</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To measure the impact of skin disease on patients' quality of life</td>
<td>To quantify the effects of a skin disease on physical discomfort and symptoms, psychologic well-being, social functioning, self-care activities, performance at work or school, and self-perceptions in patients with a certain dermatosis</td>
<td>To distinguish the burden of skin disease in different population at one point in time as well as an outcome measure to show how patient’s QoL changes as their skin disease changes over time</td>
</tr>
<tr>
<td><strong>Number of items</strong></td>
<td>10</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Adult (&gt; 15 years)</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td><strong>Mode of administration</strong></td>
<td>Self-administered</td>
<td>Self-administered</td>
<td>Self-administered</td>
</tr>
<tr>
<td><strong>Time recall</strong></td>
<td>Last week</td>
<td>Last month</td>
<td>Last month</td>
</tr>
</tbody>
</table>
2.11. Psychometric evaluation of QoL instruments

Most commonly, psychometric evaluation of QoL instruments is done through using a group of psychometric methods which are based on a two-component assumption of observed scores i.e. true score and error score. These tests are known as classical test theory (CTT) methods [51]. CTT is also known as true score model and traditional test theory [52]. They are associated with one important limitation, the raw scores used in this group of tests are "ordinal", so they cannot be used for mathematical operations. In other words, CTT measurements cannot be considered as real measurements [51, 52]. To overcome this limitation, the methods which could make variables with fundamental measurement characteristics out of the ordinal raw scores get more importance. One of these models is Rasch model which is a probabilistic model using natural logarithm of the odds (logits) of given ordinal responses to make a linear function with fundamental measurement characteristics [51-53].

Rasch model is commonly considered as a one-parameter Item Response Theory (IRT) model [51-53], but most of its proponents do not consider it as an IRT model, because Rasch’s model primary requirements are fundamental measuring ones, making it different from IRTs, which similar to other statistical modeling approaches, emphasize on the fit of a model to observed data. While adequate data-model fit is important in Rasch modeling, it is a secondary requirement to be met before an instrument can be claimed to measure a latent variable [51, 52, 54-57].

One of the major applications of the Rasch model is to evaluate the construct validity of a questionnaire by excluding unsuitable items [56].

Basic definitions related to the Rasch model are provided in the Fact Box 2.

2.12. Classical Test Theory versus Rasch model

Some characteristics of CTT and the Rasch model are compared in Table 4 [58].

2.13. Previous QoL Studies on Patients with Active CL

Before development of the protocol of the present study in 2007 [22], a comprehensive search in electronic databases including Medline via PubMed was done and resulted in retrieval of only two articles that had reported some findings related to the QoL of patients with CL. They were Yanik et al, 2004 and Reithinger et al, 2005. [59, 60]. Since then, a few more studies has been conducted to assess the QoL of patients suffering from active CL lesions.

Yanik et al. used Turkish Quality of Life (TQL) for skin diseases, also known as Dermatology Quality of Life (DQL) to measure the impact of CL on patients’ QoL [59]. They reported a mean score (standard deviation [SD]) of 34.77 (±8.47) (instrument score range: 0 to 44), in patients with active CL lesions which is much higher than the reported mean scores for all other skin diseases 14.69 (±10.28) by Gurel et al. who developed DQL and used it on different skin conditions in Turkey [61]. Since DQL was not validated using the Rasch model, it is unlikely that it had the needed properties for fundamental measurement.
Fact Box 2. Basic definitions in Rasch analysis.

- The simplest Rasch model is the dichotomous model and is defined as:
  \[ \loge(P_{ni1}/P_{ni0}) = B_n - D_i \]
  where \( P \) is the probability of answering “Yes” to the item “i” by the person “n”. \( B_n \) is an estimate of the person “n” ability based on his/her raw score, \( D_i \) is a measure of difficulty for an item based on its raw score.

- A polytomous Rasch model is defined as:
  \[ \loge(P_{ni1}/P_{ni(j-1)}) = B_n - D_i - F_j \]
  where, \( P \) is the probability of answering the item "j" by the person "ni", , and \( F_j \) is an estimate of frequency of each category. \( B_n \) and \( D_i \) have the same definition as they have in the dichotomous model.

- **Item measure**: is the Rasch model estimate of item difficulty in logits.

- **Person measure**: is an estimate of the patient’s ability based on his/her performance on a set of items e.g. a test, a QoL questionnaire, etc.

- **Fit**: is the degree of match between the pattern of the observed responses and the Rasch-modeled expectations.

- **Item fit statistics**: are indices that show the extent to which each item matches the Rasch-modeled expectations.

- **Person fit statistics**: are indices that estimate the extent to which the responses of any person conform to the Rasch-modeled expectation.

- **Infit statistics**: are weighted estimates of the statistics indicating the degree of fit of observations to the Rasch modeled-expectations. They give more value to on-target observations and are more sensitive to irregular inlying patterns.

- **Outfit statistics**: are unweighted estimates of the degree of fit of responses. These values tend to be influenced by off-target observations. They are expressed in two forms: unstandardized mean squares and standardized \( t \) values.

- **Mean Square (MnSq)***: is one of the two measures that show the degree of an item or person fit to the Rasch model. It is a transformation of the residuals, the difference between observed and predicted fit values. Its estimated value is 1.00.

- **Standardized \( t \)***: is the alternative measure indicating the match of an item or a person to the Rasch model. “Standardized” indicates that the distribution of fit values are standardized to a distribution with a mean = 0 and variance = 1 in this measure.

- **Misfit (noisy)**: Items or persons with outfit MnSq >1.3 to 1.5 or outfit \( t \) value >2 (\( P<0.05 \)). This indicates more erratic and haphazard performance than the Rasch model predict.

- **Overfit (muted)**: Items or persons with infit MnSq <0.5 to 0.7 or infit \( t \) value <-2 (\( P<0.05 \)). This indicates less variability in the data than the Rasch model predicted and generally reflects dependency in the data.

*Calculation formula has been provided in Appendix I.

Table 4. Comparison of some characteristics of classical test theory and the Rasch model [58].

<table>
<thead>
<tr>
<th>Main characteristics</th>
<th>Rasch Model</th>
<th>Classical test theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on/uses</td>
<td>Linear measures</td>
<td>Raw scores</td>
</tr>
<tr>
<td>Meaning (interpretation regarding the latent variable)</td>
<td>Linear positioning on a latent variable explicitly defined by the item content</td>
<td>Ordinal ranking on “hoped-for” latent variable</td>
</tr>
<tr>
<td>Sensitivity to missing data</td>
<td>Robust for missing data</td>
<td>Sensitive to missing data</td>
</tr>
<tr>
<td>Status (what is it really?)</td>
<td>Known as estimates</td>
<td>Mistaken for truth</td>
</tr>
<tr>
<td>Sample dependency</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

| Measuring properties                              |                                |                                            |
| Additivity                                        | Yes                             | No                                         |
| Continuity                                        | Yes (continuous)               | No (discrete)                              |
| Suitability for linear statistics                 | Ideal                           | Unsuitable                                 |
| Equation and integration                          | Simple                          | Awkward                                    |
| Accuracy                                          | Quantified by fit statistics   | Unknown                                    |
| Precision                                         | Quantified by standard errors (SE) | Unknown (except average)                 |

In a study from Iran, QoL of patients with CL was measured using Persian validated version of DLQI [62, 63]. It showed a mean (±SD) DLQI score =5.87(±5.96). The most affected and least affected domains were symptoms and feelings, and treatment with a mean=2.07(±1.50) and a mean=0.45(±0.78), respectively. In the majority of patients (71 cases, 57.3%), QoL impairment was small or none [62].

Another study using DLQI for QoL measurement of women with CL in an endemic area of Iran showed baseline DLQI mean scores of 10.6 (±5.7) and 10.0 (±5.1) in the two parallel arms of their randomized controlled trial [64], which was higher than Vares et al. reported mean of 6.4 (±6.7) reported for women [62]. This difference might be caused by the different areas of studies, most cases of CL in Kerman are caused by L. tropica, while Isfahan is endemic for L. major, which is more inflammatory and ulcerates more frequently in comparison with the former.

DLQI has also been used to evaluate QoL of patients with CL in a study conducted in Fasa, Iran, where CL due to L. major and L. tropica occurs [65, 66]. The mean DLQI score of the patients were 13.67 (±7.81), higher than what was observed in earlier cited studies from Iran [62, 64]. The most and least affected domains were symptoms and feelings (mean = 6.09[±1.74]), and treatment (mean=[1.41±0.97]), which were similar to Vares et al. findings [62]. However, in contrary to Vares et al. who reported high or extremely high effects on QoL in 18.5% of their patients, Noorpisheh et al. reported that QoL was highly or extremely highly affected in 61.4% of CL patients [65].

Ranawaka et al. [67], used DLQI to evaluate the QoL in Sri Lankan CL patients. They reported that un 21% of the patients CL had no effect on their QoL and in 86% those
whose QoL was affected, the effect was only mild to moderate [67]. They identified that feelings as the most affected domain and sexual relationship as the least affected domain and concluded that CL is an overall mild disease in Sri Lanka [67].

Khoshnood et al. [68], used Persian validated version of DLQI and reported a mean DLQI score of 11.7 (±7.5) in patients with CL in Shiraz, Iran. They identified “feelings” (1.54 of 3) and “sexual relationship” (0.42 of 3) as the most and the least affected domains, respectively [68]. They reported a significant difference in DLQI scores in patients with a high number of ulcerated lesions (13.5) than in other cases (8.1) (P<0.05), but they did not find statistically significant difference in DLQI scores between men (11.40) and women (11.99) (P=0.663) [68]. Patient’s age, duration of lesion, marital status, and occupational status did not affect patient’s DLQI score (P>0.05) [68]. While patients with active CL lesions had a higher DLQI mean score (12.6) than those with inactive healed lesions (DLQI mean score=9.31), it was not statistically significant (P=0.123) [68]. They found a low positive correlation between number of the lesions and impairment of QoL in CL patients (r=0.205, P=0.03) and also reported that patients with CL lesions on the three areas of the body, i.e., head and neck, upper body, lower body had a mean DLQI score of 24.33 which was much higher than the observed overall mean score of all studied patients [68]. According to their report, 95% of the studied patients experienced some levels of QoL impairment, most commonly (42.5%) “high” level. CL effects on QoL of patients were considered “low”, “moderate”, and “very high” in 18.2%, 16.7%, and 17.5% of patients, respectively [68].

Elsaei and Ibrahim [69] used DLQI to measure the impact of CL on patients’ QoL in Egypt and reported a DLQI mean equal to 12.67 with the symptoms and feelings being the most affected domain. They reported significant improvement of QoL in their patients after 3 to 7 sessions of treatment with pulsed dye laser (PDL) at 3-week intervals (DLQI mean score = 4.25, P<0.05) [69].

Since those studies used DLQI, a generic-dermatology QoL instrument with known problems in its fundamental measurement characteristics [70, 71], their finding have to be interpreted cautiously.

Reithinger et al. [60] conducted a survey and also interviewed with patients suffering from CL in Afghanistan. It was the only published study which was retrievable form well-known scientific journal indexing databases such as Medline and ISI Web of Science, which included qualitative approach to study patients the with CL before we decided to conduct a qualitative research on CL patients [22].
3. Study Rationale (Justification)

Globally, hundreds of millions of people are at risk of being affected by CL and more than one million new CL cases are reported each year. In many developing countries CL is prevalent and in several of them it is considered as a major health problem [4]. It is important to assess the impact of CL on the lives of this considerable population because it can potentially affect the QoL of the patients adversely by causing physical, psychological, and social problems.

Although CL is generally considered as a self-healing disease, ZCL and ACL both can adversely affect life of the patients. At its ulcerative stage, ZCL can result in discomfort and even disability, which can result in loss of working hours and wages. In addition, when ZCL lesions remained to be self-healed, they can result in disfiguring scars, lifelong stigmas usually on the exposed sites of skin. Generally, ACL lesions are more chronic and at the worst scenario, they can develop into a long-lasting, destructive and disfiguring form, known as leishmaniasis recidivans, which is very difficult to treat [3].

Yanik et al. [59] assessed the psychological impact on CL patients in an endemic area of Turkey. They reported significantly higher anxiety and depression scores, a lower body satisfaction score as well as reduced quality of life in patient with active CL in comparison with healthy controls ($P<0.05$). To assess their patients, they used the Turkish validated Hospital Anxiety Depression (HAD) and Body Image Satisfaction (BID) scales as well as a Dermatology Quality of Life (DQL) Scale which had been developed in Turkish population. They concluded that CL might affect all three dimensions of health mentioned in definition of health by the WHO [59].

In 2005, Reithinger et al. [60] published the finding of their study of social impact of CL in Kabul, Afghanistan. They reported that affected people were excluded from communal life which might range from minor restrictions such as avoidance of sharing of cups, plates and so on to more severe isolation. In addition, they reported an associated trauma from the disease in children with CL because of disfigurement, pain and discomfort associated with treatment and exclusion from playing with other children [60]. Also, some respondents noted that women with active CL or remaining scars had difficulty in finding husbands [60]. Different ways that AOWCL may adversely affect QoL of patients are summarized in Table 5.

Khatami et al. systematic review on the treatment of AOWCL showed that no PRO including QoL, was evaluated as a primary outcome in 50 included trials [25]. A Cochrane systematic review on the interventions for OWCL, published one year after Khatami et al., stated that in 2 trials of 49 included trials, QoL was evaluated as a secondary outcome [72], but a full-text review of those two trials by the PhD student showed that none of them measured QoL as even a secondary outcome [73, 74].

Development of a QoL instrument that can properly measure the impact of CL on the patients may be used as a PRO for clinical evaluation of patients and treatment triage of CL patients. This QoL instrument can be used in clinical trials as well. It can be considered as a secondary outcome in those studies.
### Table 5. Theoretical concepts of the impact of AOWCL on patients’ QoL.

<table>
<thead>
<tr>
<th>Clinical concerns</th>
<th>Subjective concerns</th>
<th>Main affected construct(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of lesion(s)*</td>
<td>Resulted anxiety ± depression for getting disease</td>
<td>Emotional</td>
</tr>
<tr>
<td></td>
<td>Anxiety ± depression about transmission the disease to others</td>
<td>Emotional</td>
</tr>
<tr>
<td></td>
<td>Anxiety ± depression about the future of disease</td>
<td>Emotional</td>
</tr>
<tr>
<td></td>
<td>Anxiety ± depression ± embarrassment for disfigurement</td>
<td>Emotional, social</td>
</tr>
<tr>
<td></td>
<td>Stigmatization</td>
<td>Emotional, social</td>
</tr>
<tr>
<td></td>
<td>Isolation</td>
<td>Social, emotional</td>
</tr>
<tr>
<td></td>
<td>Physical limitation and discomfort</td>
<td>Physical, emotional, social, economic</td>
</tr>
<tr>
<td></td>
<td>Daily activities†</td>
<td>Physical, emotional, social</td>
</tr>
<tr>
<td></td>
<td>Loss of occupation</td>
<td>Economic, emotional, social</td>
</tr>
<tr>
<td>Treatment‡</td>
<td>Expense(s)</td>
<td>Economic</td>
</tr>
<tr>
<td></td>
<td>Availability</td>
<td>Emotional, economic</td>
</tr>
<tr>
<td></td>
<td>Associated anxiety/pain</td>
<td>Emotional</td>
</tr>
<tr>
<td></td>
<td>Adverse effects</td>
<td>Physical, emotional, economic</td>
</tr>
</tbody>
</table>

*Described subjective concerns and affected constructs have been described for simple uncomplicated AOWCL lesion(s). †Including: hygiene like washing hands, bathing, and so on, housework such as cleaning and cooking, religious duties, prayers. ‡Described subjective concerns and affected constructs have been described for the treatment of uncomplicated AOWCL lesion(s). This table is based on the Yanik et al. [59], Reithinger et al. [60] findings, as well as Alireza Khatami personal experiences.

Hotez [75] discussed the importance of stigma in neglected tropical diseases and considered that its impact could not be measured appropriately using measures such as quality-adjusted life year (QALY). While the primary aim of developing a disease-specific instrument for measuring the QoL of CL patients is to measure their QoL from the patients’ point of view, and include impact of stealth factors such as stigma, however, there might be a potential role for a well-developed and standardized QoL instrument for CL, which encompasses the associated stigma, quantifies it together with other domains of QoL, and then be used for health economic studies. Estimating preference weight for a health status measured with EQ-5D, and combining the weight with time to calculate the gained QALYs and using it as an outcome in cost-utility analysis to compare the benefit and cost of health care programs or interventions is an example of how a QoL instrument could be used for health economic evaluations and help the health authorities to allocate the resources properly [76].
4. Aim and Objectives

4.1. Overall Aim

The overall aim of this study was to develop an instrument to evaluate the QoL of Iranian adult patients with AOWCL.

4.2 Specific Objectives

The objectives are:

1) To investigate the quality of therapeutic RCTs in AOWCL including assessment of the used outcome measures
2) To explore how patients perceive and experience having AOWCL
3) To develop a diseases-specific instrument for measuring QoL in AOWCL
4) To evaluate the psychometric characteristics of the developed instrument
5. Methodology

5.1. Overview of the Studies

This thesis is based on a mixed-method research consisting of two quantitative and one qualitative studies. An overview of the studies included in this thesis is provided in Table 6.

Table 6. Overview of the studies in the thesis.

<table>
<thead>
<tr>
<th>Study#1</th>
<th>Study#2</th>
<th>Study#3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the quality of therapeutic RCTs in AOWCL including measured outcomes</td>
<td>To explore how patients perceive and experience having AOWCL</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Systematic review of RCTs</td>
<td>Qualitative content analysis</td>
</tr>
<tr>
<td><strong>Data source</strong></td>
<td>Electronic databases + hand search of the relevant journals</td>
<td>Patients with AOWCL in Tehran and Kashan</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>50</td>
<td>12</td>
</tr>
</tbody>
</table>

RCTs, Randomized controlled clinical trial; AOWCL, Acute Old-World cutaneous leishmaniasis; QoL, Quality of life.

* Development of the questionnaire was started by extracting the items based on the findings of the 2nd study. †Number of the articles in study#1, and number of participants in studies #2 and #3.

The first quantitative study (study#1) was a systematic review on randomized controlled trials of the treatments of the AOWCL (Paper I), which was included in this PhD study in August 2013.

The qualitative study (study#2) was designed to understand how the patients with AOWCL experienced their disease and its impacts on their QoL. A qualitative content analysis was used for the interpretation of the collected data (Paper II).

The second quantitative study (study#3) began by including the relevant extracted items from the patients' interviews and developing the preliminary version of the CL-specific QoL instrument according to an expert panel review. Psychometric properties of the instrument were evaluated through a survey using the Rasch method (Paper III).

The methods in studies #1 to #3 are described under subtitles 5.2. to 5.4. Ethical considerations are provided under subtitle 5.5.

5.2. Methodology of Study#1 (Paper I)

This study was designed and conducted as a systematic review of the literature.

5.2.1. Search Strategy and Selection Criteria

Evidence was reviewed according to the hierarchy of evidence whereby systematic reviews of randomized controlled trials (RCTs) were considered as the most robust
evidence, followed by individual RCTs [77]. Since there was no published systematic review on CL treatment at the time of the publication of this paper, the primary source of evidence was individual RCTs. To locate all studies concerning treatment of CL, an initial sensitive search was performed using cutaneous AND leishman$ AND treat$ OR (therap$ NOT treat$) filter in Cochrane Central Register of Controlled Trials (3rd quarter 2006), Ovid MEDLINE (1966 to July 2006), and EMBASE (1980 to July 2006). Early online and other electronic formats of articles were also searched and considered. No language limitation was considered. A hand search was also performed on all available issues of medical journals that were published in Iran up to June 2006. In addition, references of relevant articles and reviews were manually searched for additional sources. Bibliographies of retrieved publications were reviewed to identify sources not found implementing the described searches. To be eligible for inclusion in the review, the studies had to be RCTs, conducted in an endemic area for Old World CL unless there were confirmatory evidence in the study that the patients had Old World CL, and the interventions had to be therapeutic.

5.2.2. Data Extraction and Critical Appraisal

The titles and available abstracts of relevant articles, which remained after omitting the duplicated ones, were reviewed and those related to acute Old World CL were selected. Among selected articles, RCTs were chosen for full text review. The authors independently reviewed all eligible articles and disagreements were solved by an all-author consensus. A modified version of a data extraction form suggested by the Cochrane Skin Group for critical appraisal was used for data were extraction (Appendix A of Paper I).

For each article a critically appraised topic (CAT) was developed, which included the article’s citation, research question, clinical bottom line, study design, characteristics of experimental and control groups, validity criteria, importance criteria, applicability, and the abstract. To minimize controversies concerning the quality of studies, the Jadad scale was used to evaluate randomization, blindness, and intention-to-treat analysis. According to the used scale, 4 and 5 scores were considered as good-quality, 2 and 3 as fair-quality, and 1 and 0 as poor-quality studies [78]. The results of quality assessment are presented in Appendix B of Paper II.

5.3. Methodology of Study#2 (Paper II)

5.3.1. Study Design and Setting

We designed a qualitative study using individual in-depth interviews as the data gathering method to get perspective of the patients with CL. To capture the manifest and latent meanings of their lived experiences, data were analyzed using qualitative content analysis approach [79]. Since we wanted to represent experiences from patients living in CL endemic (Kashan) and non-endemic (Tehran) areas of Iran, the study was conducted at two different sites in Iran: Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), a referral research center for CL patients from all over the country with about referred 140 CL patients per year [80], located in Tehran, and Golabchi Clinic in Kashan about 210 kilometer south of Tehran, where CL is endemic [81].
5.3.2. Sampling of Informants

We aimed to capture the experiences from both genders from different socio-economic strata and to reach maximum variation in regards to the severity of the participants’ disease, so we used a purposive sampling method. According to expert opinions and for practical reasons, CL severity was categorized in three levels: mild, moderate and severe. Patients with more than 5 lesions, lesions larger than 50 mm in the largest diameter of induration, ulcerative lesions on the face, and sporotrichoid lesions (clinical description of CL lesions which consist of a primary lesion combined with lymphangitis and nodules and/or ulcerated lesions along the lymphatic vessels [82]) were classified as "severe" cases. Patients with only one or 2 lesions with the largest diameter less than 30 mm on locations other than face and ears were considered as "mild" cases and patients with in between lesion number and size were defined as cases with "moderate" disease.

The eligibility criteria were provided to the healthcare providers responsible for CL patients at both clinics in Tehran and Kashan. When they found an eligible patient who was interested in participating in the study, they informed the PhD student who went to the CL clinic, met the patient in person, performed the clinical evaluation and if he found the patient eligible for the study too, the aim of the study was explained to him/her and the time and place for the interview were set.

5.3.3. Data Collection and Analysis

Data collection took place during October 2010 to November 2011. Before starting the interviews, the informants were asked to provide written consent and permission to voice recording. All interviews were conducted by the PhD student at the respective clinics in rooms that allowed for privacy. All interviews were digitally recorded and followed a thematic guide including three main content areas: "disease development", "living with the disease", and "treatment and healthcare" (Appendix II). During and after the interviews reflective notes were taken by the interviewer to facilitate elaboration on important issues in the forthcoming interviews. The interviews took between 40-75 minutes.

In total, twelve interviews were held with three men and three women recruited at CRTSDL and three men and three women at Golabchi Clinic. These interviews were regarded sufficient to capture the range of experiences and in the last interviews not much new information emerged.

All interviews were transcribed verbatim into Persian and later translated into English to facilitate joint analysis within the research group. The analysis followed the procedures suggested by Graneheim and Lundman [79]. The identified meaning units were condensed before coding the text. Then, the codes were clustered and categories and subcategories were developed to capture the manifest meaning of the text. Finally, themes were constructed to interpret the more latent meaning. During the analysis process the interpretation was continuously discussed in the research group. An example of the process of analysis from condensed meanings to codes, subcategories, and categories has been demonstrated in Table 7.
Table 7. Example of analysis process from condensed meaning units to categories.

<table>
<thead>
<tr>
<th>Condensed meaning unit</th>
<th>Code</th>
<th>Subcategory</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;I became sad when I got CL. Probability of remaining scars is annoying&quot;</td>
<td>Becoming sad, fearing remaining scars</td>
<td>Becoming sad</td>
<td>Sensing responsibility</td>
</tr>
<tr>
<td>&quot;When I see people avoiding me because of my CL, or when they think it is communicable, I feel sad.&quot;</td>
<td>People avoid me, think it is communicable, making me sad</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;My lesion's appearance is awful. I dislike it&quot;</td>
<td>Disliking own appearance</td>
<td>Reacting with self-disgust</td>
<td></td>
</tr>
<tr>
<td>&quot;I became angry after I got CL&quot;</td>
<td>Becoming angry</td>
<td>Feeling angry</td>
<td></td>
</tr>
<tr>
<td>&quot;I regret that I did not use a bed net and I got CL&quot;</td>
<td>Regretting not using bed-net</td>
<td>Regretting own acts</td>
<td></td>
</tr>
</tbody>
</table>
5.4. Methods of Study#3 (Paper III)

5.4.1. Study Setting, Design and Sampling

This study was designed as a survey. It was conducted at the same two sites where the qualitative study was conducted. Based on a consecutive sampling method, patients of both sexes with any severity of CL were recruited into the study. CL severity was defined according to the same criteria used in the second study.

According to the suggestion by Linacre [83] a sample size of 100 is suitable for most purpose when there is 95% confidence interval (CI) and the item calibrations or person measures stable within ± 1/2 logit.

5.4.2. Participants and Eligibility Criteria

Inclusion criteria were: i) ≥18 years old, ii) parasitologically confirmed CL, and iii) willingness to participate. Exclusion criteria were: i) lesion duration for >6 months, ii) existing significant psychiatric problem that might result in unreliable answers to the questions, and iii) underlying significant medical conditions that could confound answering the questions such as end-stage renal disease or metastatic cancer. After screening for the eligibility criteria and before being recruited into the study, the overall aim of the study was explained by a member of the research team to the potential participants and the patients were asked for written consent.

Then, demographic and clinical data including age, sex, occupation, socio-economic status of the patients, as well as location of the lesion(s), duration of the lesion(s), number of the lesions, and size of the lesion(s) were recorded on a Case Report Form (CRF) developed specifically for this study (Paper III, Appendix A). The Persian version of the developed questionnaire for measuring QoL in CL patients was given to the patients too. A member of the research team was present during the whole session and was ready to help the patients if they need any explanation for answering the QoL questions.

5.4.3. Development of the Preliminary Version of the QoL Questionnaire for CL

Based on the interviews conducted with the CL patients in the second study, a QoL questionnaire was first developed in English from the items pool. Then it was translated into Persian and compared to the original English version. This version was sent to an expert panel for CL in Iran and they suggested few minor revisions. After making the requested revisions, the questionnaire had 50 questions and each item was to be scored using a four-point Likert scale (Paper III, Appendix B). This preliminary version of the CL QoL instrument was administered to the patients and also was back-translated to English.

5.4.4. Data Collection

Data collection took place during September 2012 to December 2014. Each session including the clinical evaluation, recording the demographic and clinical data, and answering the QoL questionnaire by the patients took from 45 to 75 minutes.
5.4.5. Statistical Methods

All collected data were entered into a dataset specifically developed for this study using version 17.0 of SPSS (SPSS Inc., Chicago, IL, USA). The continuous variables were summarized with mean ± standard deviation (SD) if their distribution was normal and with median (inter-quartile range [IQR]) if their distribution was not normal. The nominal and ordinal variables were reported as frequencies and relative frequencies (percentage).

A Rasch analysis was done following the procedures suggested by Bond and Fox [52]. After preparing the SPSS file for being used by Winsteps (Winstep ©, John M. Linacre, Chicago, IL., USA) version 3.75, the latter was used for doing Rasch analysis. A polytomous Rasch model was used to change the raw scores to logits.

Using Rasch measurement, fit measures were obtained for the whole baseline dataset of 107 participants (persons) and 50 questions (items). Since the items had a four-point Likert scale response option, a Rating Scale Analysis (RSA) was applied [84]. Targeting, person fit, category and threshold ordering, item fit, and Differential Item Functioning (DIF) analyses were performed. Unfitted items and persons were removed and another round of analyses were done on the remaining persons and items. Person and item fit measures and model summary statistics were reported in tables, graphs, and figures.

5.5. Ethical Considerations

Since the study protocol of the PhD study and its attachments were reviewed by the Ethical Committee of Research in Medical Sciences of CRTSDL, Tehran University of Medical Sciences, Tehran, Iran, the second and third studies had the same clearance, received on December 1, 2007.

Before recruitment, a member of the research team gave the informed consent form to each eligible participant. The informed consent form clearly indicated how the participant’s confidentiality would be kept and that the participation was voluntary and would not influence the medical treatment. Literate participants were asked to read the form carefully and were provided with further clarifications if needed before signing the form. Illiterate participants were given the same information orally. After answering their questions and being ensured that the participant understood the content, the research team member obtained his/her fingerprint as consent of participation. Both studies were conducted in accordance with the Declaration of Helsinki [85].
6. Results

6.1. Outcomes Reported in CL RCTs (Paper I)

Fifty RCTs met inclusion criteria consisting of 5515 patients in 119 study arms. Reviewed trials were highly variable in quality and methods and generally provide weak evidence for treatment of acute Old World CL.

The interventions that were used in the treatment of AOWCL showed a huge diversity and were resulted a wide spectrum of efficacies, which indicated that no single safe intervention was acceptable for treating CL. The overall low quality of the majority of the included trials as well as the observed significant heterogeneity in regard to outcome definition in those studies, resulted in another important finding of this systematic review, which was the absence of including any PRO measure in general, and QoL measurement in particular, in the reviewed studies.

Table 8 demonstrates the summary of primary, secondary, and tertiary outcomes measures used in different RCTs on the treatment of AOWCL, which has been published up to July 2006.

Table 8. Primary, secondary, and tertiary outcome measure in CL RCTs.

<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Country</th>
<th>Primary Outcome</th>
<th>Secondary and Tertiary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Asilian and Davami (2006) [86]</td>
<td>Iran</td>
<td>Complete improvement: No sign of induration, inflammation, and complete re-epithelialization + PC</td>
<td>Adverse effects, prevention of scarring, PC or histopathological cure</td>
</tr>
<tr>
<td>2 Firooz et al. (2006) [87]</td>
<td>Iran</td>
<td>Clinical cure: &gt;75% reduction in size of lesions compared with baseline 8 weeks after treatment</td>
<td>Adverse effects, duration of remission and % recurrence within six months,</td>
</tr>
<tr>
<td>3 Sadeghian and Nilforoshzadeh (2006) [88]</td>
<td>Iran</td>
<td>Complete improvement: Lesions had been flattened, no induration and epidermal creases had appeared</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>4 Crawford et al. (2005) [89]</td>
<td>Iran</td>
<td>Response to treatment: decrease in size of erythema, induration, and ulceration</td>
<td>-</td>
</tr>
<tr>
<td>5 Famili et al. (2005) [90]</td>
<td>Iran</td>
<td>Complete cure: Disappearance or reduction of &gt;75% in lesion size + PC</td>
<td>No 2nd outcome was defined</td>
</tr>
<tr>
<td>6 Firooz et al. (2005) [91]</td>
<td>Iran</td>
<td>Complete re-epithelialization of each ulcer with marked reduction in induration ± scarring</td>
<td>Adverse effects, % recurrence within six months, volume of injected medicine</td>
</tr>
</tbody>
</table>
Table 8. (Cont’d).

<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Country</th>
<th>Primary Outcome</th>
<th>Secondary and Tertiary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Iraji and Sadeghinia</td>
<td>Iran</td>
<td>Complete healing: Reduction in size and induration of lesion(s) by at least 75%</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>(2005) [92]</td>
<td></td>
<td>and amastigotes free lesion smears</td>
<td></td>
</tr>
<tr>
<td>8 Nassiri-Kashani et al.</td>
<td>Iran</td>
<td>Response: Cure (complete re-epithelialization of all lesions) or improvement</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>(2005) [93]</td>
<td></td>
<td>(reduction in size of lesion)</td>
<td></td>
</tr>
<tr>
<td>9 Reithinger et al.</td>
<td>Afghanistan</td>
<td>Complete cure: Complete re-epithelialization of CL lesions without any signs of</td>
<td>Adverse effects, time to be cured</td>
</tr>
<tr>
<td>(2005) [73]</td>
<td></td>
<td>induration</td>
<td></td>
</tr>
<tr>
<td>10 Nilforoushzadeh et al.</td>
<td>Iran</td>
<td>Complete cure: Complete clinical cure + PC</td>
<td>No 2nd outcome was defined.</td>
</tr>
<tr>
<td>(2005) [94]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Sadeghian et al.</td>
<td>Iran</td>
<td>Complete cure: Complete disappearance of induration and re-epithelialization</td>
<td>Adverse effects, duration of remission and recurrence after three months, PC or histopathological cure</td>
</tr>
<tr>
<td>(2005) [95]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Shazad et al. (2005)</td>
<td>Iran</td>
<td>Complete cure: Complete re-epithelialization of all lesions 1 week after</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>[96]</td>
<td></td>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td>13 Asilian et al. (2004)</td>
<td>Iran</td>
<td>Effective treatment: Surface re-epithelialization, flattening of lesion + PC</td>
<td>Adverse effects, time taken to be cured, prevention of scarring</td>
</tr>
<tr>
<td>[97]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Asilian et al. (2004)</td>
<td>Iran</td>
<td>Cure: Complete re-epithelialization and disappearance of edema, induration, and</td>
<td>Adverse effects, duration of remission and % recurrence within, six months, PC or histopathological cure</td>
</tr>
<tr>
<td>[98]</td>
<td></td>
<td>other signs of inflammation + PC</td>
<td></td>
</tr>
<tr>
<td>15 Iraji et al. (2004)</td>
<td>Iran</td>
<td>Cure: Total clearance of lesion + PC, or marked improvement: Reduction in size ≥60%</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>[99]</td>
<td></td>
<td>+ PC</td>
<td></td>
</tr>
<tr>
<td>16 Nilforoushzadeh et al.</td>
<td>Iran</td>
<td>Cure: Complete re-epithelialization and disappearance of edema, induration, and</td>
<td>No 2nd outcome was defined</td>
</tr>
<tr>
<td>(2004) [100]</td>
<td></td>
<td>other signs of inflammation</td>
<td></td>
</tr>
</tbody>
</table>
### Table 8. (Cont’d).

<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Country</th>
<th>Primary Outcome</th>
<th>Secondary and Tertiary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 Asilian et al. (2003) [101]</td>
<td>Iran</td>
<td>Cure: Complete re-epithelialization and disappearance of edema, induration, and other signs of inflammation + PC</td>
<td>Adverse effects, duration of remission and % recurrence within, six months, PC or histopathological cure</td>
</tr>
<tr>
<td>18 Asilian et al. (2003) [102]</td>
<td>Iran</td>
<td>Cure: Clinical improvement ± PC</td>
<td>Adverse effects, PC or histopathological cure</td>
</tr>
<tr>
<td>19 Faglihi and Tavakolikia (2003) [103]</td>
<td>Iran</td>
<td>Complete cure: Re-epithelialization and return to normal in skin texture in 2 months with no residual scar or relapse after 1-year of follow-up</td>
<td>Duration of remission and % recurrence within one year, prevention of scarring</td>
</tr>
<tr>
<td>20 Momeni et al. (2003) [104]</td>
<td>Iran</td>
<td>Definitive cure: All lesions were healed + PC</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>21 Nilforoushzadeh et al. (2003) [105]</td>
<td>Iran</td>
<td>Complete cure: Complete disappearance of induration and re-epithelialization</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>22 Alrajhi et al. (2002) [106]</td>
<td>Saudi Arabia</td>
<td>Complete cure of all lesions</td>
<td>Adverse effects, time to be cured</td>
</tr>
<tr>
<td>23 Esfandiarpour and Alavi (2002) [74]</td>
<td>Iran</td>
<td>Cure: Excellent response (≥80% reduction in size of lesion or complete cure [subsidence of inflammation, edema, and flattening of lesions]) or good response (reduction of lesion size by 50%)</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>24 Momeni et al. (2002) [107]</td>
<td>Iran</td>
<td>Definitive cure = all lesions healed + PC</td>
<td>Adverse effects, PC or histopathological cure</td>
</tr>
<tr>
<td>25 Mapar et al. (2001) [108]</td>
<td>Iran</td>
<td>Complete healing or cure = considerable (not exactly defined) reduction in size, induration, and inflammation of lesion + PC</td>
<td>No 2nd outcome was defined.</td>
</tr>
<tr>
<td>26 Salmanpour et al. (2001) [109]</td>
<td>Iran</td>
<td>Cure: Complete re-epithelialization of lesions with little or no scarring at 6 weeks after treatment</td>
<td>Adverse effects</td>
</tr>
</tbody>
</table>
Table 8. (Cont’d).

<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Country</th>
<th>Primary Outcome</th>
<th>Secondary and Tertiary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 Sharqie et al. (2001) [110]</td>
<td>Iraq</td>
<td>Cure: Total clearance of lesion + PC, or marked improvement; Reduction in size ≥60% + PC</td>
<td>Adverse effects, prevention of scarring, time to be cured</td>
</tr>
<tr>
<td>28 Vardy et al. (2001) [111]</td>
<td>Israel</td>
<td>Lesions measured; difference before and after treatment (Δmm²)</td>
<td>-</td>
</tr>
<tr>
<td>29 Gholami et al. (2000) [112]</td>
<td>Iran</td>
<td>Complete healing + PC</td>
<td>No 2nd outcome was defined</td>
</tr>
<tr>
<td>30 Kocher et al. (2000) [113]</td>
<td>India</td>
<td>Complete healing and disappearance of lesion on reversible hypopigmentation at lesion site</td>
<td>Adverse effects, PC or histopathological cure</td>
</tr>
<tr>
<td>31 Mujtaba and Khalid (1999) [114]</td>
<td>Pakistan</td>
<td>Vaguely defined “complete cure”</td>
<td>Adverse effects, time to be cured, duration of remission and % recurrence within six months, one, two and three years (no statement on time assessment), prevention of scarring</td>
</tr>
<tr>
<td>32 Alkhawajah et al. (1997) [115]</td>
<td>Saudi Arabia</td>
<td>Vaguely defined clinical outcome</td>
<td>Adverse effects, prevention of scarring</td>
</tr>
<tr>
<td>33 Zerehsaz et al. (1999) [116]</td>
<td>Iran</td>
<td>Complete cure: Clinical improvement with complete healing, re-epithelialization of lesion(s)</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>34 Ozgostasi and Baydar (1997) [117]</td>
<td>Turkey</td>
<td>Cure: Complete healing + disappearance of lesion or incomplete healing: (reduction in size of lesion + PC)</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>35 Sharqie et al. (1997) [118]</td>
<td>Iraq</td>
<td>Cure: Total clearance of lesion + PC, or marked improvement: Reduction in size ≥60% + PC</td>
<td>Adverse effects, time to be cured</td>
</tr>
<tr>
<td>36 Dogra and Saxena (1996) [119]</td>
<td>India</td>
<td>Clinical Cure: Cured 3 months after treatment (no specific definition)</td>
<td>Adverse effects, PC or histopathological cure</td>
</tr>
<tr>
<td>37 Momeni et al. (1996) [120]</td>
<td>Iran</td>
<td>Definitive cure all lesions cured + PC</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>Study (Year of Publication)</td>
<td>Country</td>
<td>Primary Outcome</td>
<td>Secondary and Tertiary Outcomes</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>38  Alsaleh et al. (1995)</td>
<td>Kuwait</td>
<td>Complete cure: &gt;90% improvement (re-epithelialization, inflammation, size) + PC</td>
<td>Adverse effects, duration of remission, and % recurrence within six months</td>
</tr>
<tr>
<td>39  Asilian et al. (1995)</td>
<td>Iran</td>
<td>Definite cure = complete re-epithelialization on day 45 or 105</td>
<td>Adverse effects, PC or histopathological cure</td>
</tr>
<tr>
<td>40  Ben Salah et al. (1995)</td>
<td>Tunisia</td>
<td>PC + clinical improvement (any degree of re-epithelialization and at least 50% reduction in size) on day 45</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>41  Larbi et al. (1995)</td>
<td>Saudi Arabia</td>
<td>Satisfactory response: Fully healed (completely healed lesions + PC) or size reduced (reduction in infiltration, erythema and size)</td>
<td>Adverse effects</td>
</tr>
<tr>
<td>42  el-On et al. (1992)</td>
<td>Israel</td>
<td>PC and clinical Cure: PC followed by complete healing of lesion at end of therapy</td>
<td>-</td>
</tr>
<tr>
<td>43  Lynen and Van Damme (1992)</td>
<td>Sudan</td>
<td>Cure: Lesion completely closed and covered with scar tissue, w/o possibility to evoke secretions on pressure + sustaining apparent cure for &gt;2 weeks</td>
<td>Adverse effects, duration of remission and % recurrence 20 to 35 days after cure</td>
</tr>
<tr>
<td>44  al-Fouzan et al. (1991)</td>
<td>Kuwait</td>
<td>Excellent: &gt;80 reduction of lesion size up to complete clearance</td>
<td>Adverse effects, duration of remission and % recurrence within 1, 2 and 3 years</td>
</tr>
<tr>
<td>45  Dogra (1991)</td>
<td>India</td>
<td>Cure: Complete disappearance of induration/redness in nodular form or complete healing in ulcerative form + 3 consecutive NSs at 10-day intervals after completion of therapy, the first immediately after end of therapy</td>
<td>Adverse effects, PC or histopathological cure</td>
</tr>
</tbody>
</table>
Table 8. (Cont’d).

<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Country</th>
<th>Primary Outcome</th>
<th>Secondary and Tertiary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>46 Harms et al. (1991) [129]</td>
<td>Syria</td>
<td>Complete healing: smooth scar and undetectable number of parasites</td>
<td>Adverse effects, PC or histopathological cure</td>
</tr>
<tr>
<td>47 Dogra et al. (1990) [130]</td>
<td>India</td>
<td>Cure: Complete disappearance of induration or redness in nodular form, or complete healing in ulcerative form + 3 consecutive NSs at monthly intervals after completion of therapy</td>
<td>Adverse effects, duration of remission, recurrence within three months., PC or histopathological cure</td>
</tr>
<tr>
<td>48 el-Safi et al. (1990) [131]</td>
<td>Sudan</td>
<td>Vaguely defined clinical outcome</td>
<td>-</td>
</tr>
<tr>
<td>49 Trau et al. (1987) [132]</td>
<td>Israel</td>
<td>Significant improvement: decrease in lesion diameter of at least one fourth of original size</td>
<td>-</td>
</tr>
<tr>
<td>50 Dogra et al. (1986) [133]</td>
<td>India</td>
<td>Cure: Complete disappearance of induration or redness in nodular form or complete healing in ulcerative form + PC</td>
<td>-</td>
</tr>
</tbody>
</table>

PC, parasitological cure; NSs, negative skin smears.

6.2. CL Patients’ Experiences (Paper II)

To explore the lived experiences of the patients with CL and how they perceived their disease as comprehensive as possible, a maximum variation sampling method was used. Both male and female patients with all degrees of severity of disease were recruited into the study. The results of using the purposive sampling to get the patients with maximum variation in their experience with CL are summarized in Figure 10. Demographic and clinical characteristics of the participants have also been shown in the same figure.

All participating patients had got CL in an endemic area. Those who lived in Tehran had got it during travels to known endemic areas of Damghan, Mashhad, Shiraz, and Zavereh. However, those who got it in Kashan had got it in Kashan or one of its suburbs named Ravand.

Comparison between the participants’ experiences was not intended in this study, so getting to the point of saturation was decided when there was no new relevant information regarding the overall experiences related to the disease.

Analysis of the interview texts demonstrated four main themes: "Fearing an agonizing disease", "Taking on the blame", "Struggling to cope", and "Longing for being seen and heard". Patients’ experiences were correlated to three content areas: disease development,
living with CL, and encountering the healthcare and community. The overview of the study finding are demonstrated in Figure 11.

**Figure 10.** Summary of the results of the used maximum variation sampling, and demographic and clinical characteristics of the participants in the qualitative study.
Figure 11. Summary of the main finding of the qualitative content analysis. Constructed themes, and the categories and subcategories contributed to their development.
Fearing an agonizing disease

This theme captured patients' worries when they experienced the early symptoms and signs of CL and how the patients perceived those experiences as frightening and threatening. The supporting categories showed how some of the clinical characteristics and the course of CL lesions could affect the patient's mental status. This theme came from early experiences of the patients during their CL ordeal and was based on two contributing categories: “Understanding the disease gradually” and “Feeling the disease's mental impact”.

Understanding the disease gradually

Early CL lesions resemble a wide spectrum of other skin disorders including but not limited to simple insect bites, boils, or allergic reactions. Most interviewees had mistaken the early phases of their disease with one of those more common disease, which usually has a shorter natural course in comparison with CL, and also respond to administrated treatments quite rapidly. However, CL did not follow the usual courses of those aforementioned diseases, which were expected to heal within a few days. That unexpected clinical course even became more complicated when the patients noticed that their lesions grew instead of healing. This enlargement and progression of the lesions despite receiving treatment for the earlier diagnoses made the patients worried. Consequent development of relatively big, red, wounded, sometimes painful skin lesions resulted in patients' confusion. From this point forward, they began to think they had got a serious skin disease, which caused worrying. This experience was more commonly narrated by those patients who had no previous knowledge about the disease and had not seen CL in their relatives or acquaintances. So, while this experience seemed to be closely associated with physical features of CL, it clearly affects patients’ minds. It is evident in what a 27-year-old man with severe CL mentioned in an interview session:

"... It was itching and red, then it became larger, like the size of a pea. It was itching and burning. After two months it became larger and still was itching. Then it became purulent. I tried to drain the purulent material myself several times, but each time the wound appears again and become purulent."

Feeling the disease's mental impact

Different experiences contributed to the CL-induced mental trauma. Some patients were scared because they misdiagnosed their own disease with more serious contagious, stigmatizing, and difficult to manage disease such as HIV/AIDS and leprosy.

Sometimes, CL was misdiagnosed by the healthcare professionals which escalated patients’ anguish. For example, one patient remembered that a general physician made a misdiagnosis of a mosquito bite and prescribed him some antihistaminic tablets and an anti-pruritic ointment, which were not effective. Patients' experiences with CL course and uncertainty about its outcome can be described as distressful. Not surprisingly, most patients felt relieved when the diagnosis of CL was confirmed in their case.

However, some patients continued to worry about long-term outcomes such as remaining scars:
"I was anxious for myself because of uncertainty about the condition [I got] and what will happen to it. ... I was relieved after CL diagnosis was made because of knowing that it was curable. However, I was worrying about the remaining [CL] scar". A 48-year-old female teacher with moderate CL from Tehran said.

Patients’ experiences indicated that having limited knowledge about CL transmissibility also contributed to the mental impact of the disease. Some participants acknowledged that the limited knowledge they had about their disease was a contributing factor to their experience of anxiety.

Patients with CL might experience physical limitations caused by the clinical characteristics of the CL lesions, which interfered with doing their jobs. Two men, both with mild CL, but one from Tehran and the other one from Kashan, had such experiences.

Caused by isolation, rejection, and even stigmatization, CL could result in social limitations too. CL-associated physical and social limitations increased mental impact of the disease.

**Taking on the blame**

This theme is one of two themes that showed how patients experienced living with CL. “Taking on the blame” represented the internal aspects of living with CL. There were two categories contributing to this theme: “sensing responsibility” and “facing stigma”.

**Sensing responsibility**

Regretting own acts such as not using a bed net when the patient was supposed to do, showed how some CL patients acknowledged their own role in getting the disease and experienced responsibility for what happened to them. These experiences were close to experiencing guilt and fault, which were associated to blame.

Several interviewees said that they felt anger, which damaged their relations with their close family members, relatives, friends and co-workers. Patients felt responsible for doing something they were expected not to do, or because of not doing something that they supposed to do as a result of their anger.

Reacting with self-disgust and becoming sad were other sub-categories contributing to “sensing responsibility”.

**Facing stigma**

Some prominent experiences in CL patients were feelings of being rejected, isolated, and excluded. These experiences showed both enacted and felt stigmatization:

"...Everyone is scared of CL. Like in the mosque that I used to go, there was a woman who had CL where everybody could see her lesions. Nobody would sit beside her or shake hands with her. People pointed her out to each other and talked about her. ... She was lonely. ... When they stood in lines for prayers (Namaz), people stood away from her in a distance...When I got CL, I experienced these matters myself.", a 23-year-old female university student with severe CL in Kashan said.
In some cases, the feelings were so overwhelming that the patients felt being stigmatized and used the exact word of stigma or being stigmatized to describe their situation.

**Struggling to cope**

This theme also reflects patients' experiences of living with CL. However, while the theme "taking on the blame" basically refers to patients' own role, "struggling to cope" illustrates how CL patients' react to other people reactions, one of the less explored aspects of the CL patients. CL patients' interactions with others were spread over a wide spectrum of somewhat contradictory experiences illustrated by two main strategies used to handle others reactions towards their disease. This theme has also two categories: “preventing others’ reactions” and “internalizing reactions from others”.

**Preventing others’ reactions**

The most common form of implementing this strategy was that patients tried to prevent the others to react to their disease through hiding the lesion or even themselves. Some other patients chose to tell lies to avoid others’ reactions.

**Internalizing reactions from others**

Another strategy that was used by some patients was trying to see the disease through the eyes of others. Through using this strategy some patients’ mentioned that they could “understand” why the others reacted to their disease in an unpleasant manner. However, some other patients could not understand or find a rationale for others' reactions, so they did not use the word “understanding” when they shared their experiences during the interviews. They used the phrase: "tolerating others’ reactions" or its synonyms, indicating that they tried to accept their situation even though they could not find out why it happened to them. It was interesting that several patients mentioned that they experienced others' support even when there were some annoying reactions.

**Longing for being seen and heard**

This theme reflects CL patients' encounter with the healthcare system. They experienced being ignored, and excluded from shared decision making for treatment plans, and not receiving proper acknowledgement for their own treatment demands. This theme is also related to the patients' experiences in the communities where people had limited knowledge about CL. Interestingly, in some cases the patients’ experiences indicated that even in the settings where people were familiar with the CL and had good information about different aspects of its contagiousness and clinical features did not grant proper attitudes towards CL patients and they were subjected to mistreatment and prejudice. This theme derived from a wider spectrum of experiences and unlike the previous themes had three categories: “finding treatment difficult but acceptable”, “noting limited knowledge on CL” and “urging for prevention”.

**Finding treatment difficult but acceptable**

According to the participants, CL treatment was an unpleasant experience, because it was associated with side effects most commonly local pain at the site of injection of the recommended first choice treatment, pentavalent antimonite slats. Their experiences showed that the treatment could be considered difficult. However, they also mentioned
when they felt that the treatment would be beneficial for them, they accepted the recommended treatment. Some patients were prepared to tolerate quite painful complications in order to quicken the healing phase.

Some patients with severe CL mentioned that disease could become annoying and putting which also results in seeking medical care.

Feeling of not playing enough roles in making decision about the treatment of their disease and being unsatisfied with their physicians’ approach to the treatment was experienced by a number of interviewees. They wanted to be more involved in the process of the treatment of their disease even if they found the treatment results satisfactory.

"I have to raise one point; my physician postponed my treatment for 10 days, because he did not want to treat me with [meglumine antimonite (MA)] injections at first. He told me that the injections would be very painful and I might not be able to walk for some time after I received the [MA] injections, but when I received the injections, they were nothing extraordinary. I think that if he started my treatment earlier, my disease would not become so bad. I imagine patients do not actively participate in choosing the treatment methods. They play too little role in the treatment plan.

", a 45-year-old housewife from Tehran who had moderately severe CL said during her interview.

**Noting limited knowledge on CL**

Patients described how they noticed unawareness about CL in their communities and elaborate on how they found this problem as was one of the most important factors increasing their suffering from their disease.

It was interesting that the community was not the only setting where the participants exposed to ignorance about their disease. A number of them encountered ignorance in the least expected setting, i.e., within the healthcare system. The consequent suspicion of that unawareness about CL among the healthcare givers resulted in patients’ experiences of inappropriate approaches towards them such as taking unnecessary cautions needed for highly transmissible disease and even refusing to provide the needed services like injections to the patients by the healthcare professionals.

Some participants had substantial suggestions on how to community awareness could be increased, underlining that the provided information had to be repeated regularly to make a real difference. Others emphasized the importance of adjusting the information that had to be provided to different groups of people including writing in simple and understandable language with minimum medical jargons, using billboards, and making animations.

**Urging for prevention**

The participants also emphasized the need for prevention. For those participants who were less economically privileged, the urge for prevention was based on the high treatment costs. However, the need for prevention was not raised only by the poor and because of economic problems. Patients from the households with moderate to high incomes also described preventive measures important and considered current preventive methods as unsatisfactory.
Figure 12 summarizes the chronological relationship of the patients’ experiences with the clinical course of the CL. Themes have been used as surrogates to the experiences.

<table>
<thead>
<tr>
<th>Longing for being seen and heard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Struggling to cope</td>
</tr>
<tr>
<td>Taking on the blame</td>
</tr>
<tr>
<td>Fearing an agonizing disease</td>
</tr>
</tbody>
</table>

**Figure 12.** Chronological relationship between the experiences (themes) and the clinical course of the disease. The gradient shading demonstrates the most likely timing and of the experience.

### 6.3. Development of a Disease-Specific Instrument for Measuring QoL in patients with AOWCL (Paper III)

The original English questionnaire developed from the patients’ perspectives expressed in the interviews conducted in the qualitative content analysis study had 49 questions. This questionnaire was translated into Persian and reviewed by a panel of Iranian experts on CL, who suggested for some minor changes in wording and adding one more question: “Has/have your lesion(s) "reduced your self-esteem"?”. This version was back translated to English and its Persian version was used in the psychometric evaluation study. It was named **Preliminary Cutaneous Leishmaniasis Quality of Life instrument (P-CL-QoL)**. Each item was to be scored using a four-point Likert scale.

A total of 360 CL cases were admitted to two clinics in Tehran and Kashan, of which 112 were found eligible for the study after eligibility screening. The main reason for exclusion was age. One hundred and thirty-nine cases were younger than 18 years old. Forty-one patients had lesions that were present longer than 6 months. Twelve patients were not recruited because of presence of underlying health conditions that could potentially affect their responses. Fifty-six patients did not participate in the study because they did not
have enough time. Of the 112 recruited patients, for 107 participants complete clinical and demographic data were gathered.

Most patients (72.1%) were recruited in Kashan and fifty-five (51.5%) of the participants were male. The median (interquartile range [IQR]) age of the patients was 36.0 (25) years, and the majority of them (51.4%) described their socio-economic status (SES) as “moderate”. Thirty-four (31.8%) patients reported their SES as “low”, and only 4.6% of them considered their SES “high”. Thirteen participants (12.2%) preferred to not mention their SES. Clinically, most patients (56.1%) suffered from mild CL, followed by 22.4% suffering from moderate and 21.5% having severe disease. The medians (IQR) of the number and duration of the lesions were 2 (2.0) and 12 (12.0) weeks, respectively. There was no correlation between the demographic and clinical characteristic of the patients.

6.3.1. Rasch Characteristics of the Original Instrument

The first step in the psychometric evaluation study was analyzing the original 50-question, four-point Likert scale instrument i.e., P-CL-QoL, using a rating scale model (RSM) Rasch method. Item characteristics of this analysis are reported in Table 9.

Table 9. Items characteristics according to the Rasch analysis of P-CL-QoL.

<table>
<thead>
<tr>
<th>Item</th>
<th>Difficulty Measure (SE)</th>
<th>Infit</th>
<th>Outfit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 General health status</td>
<td>0.46 (0.15)</td>
<td>1.12</td>
<td>0.9</td>
</tr>
<tr>
<td>2 Painful lesion(s)</td>
<td>-0.01 (0.16)</td>
<td>1.17</td>
<td>1.2</td>
</tr>
<tr>
<td>3 Burning sensation of the lesion(s)</td>
<td>-0.16 (0.15)</td>
<td>1.16</td>
<td>1.1</td>
</tr>
<tr>
<td>4 Itching lesion(s)</td>
<td>-0.32 (0.16)</td>
<td>1.23</td>
<td>1.5</td>
</tr>
<tr>
<td>5 Foul-smelling lesion(s)</td>
<td>1.54 (0.32)</td>
<td>0.75</td>
<td>-0.3</td>
</tr>
<tr>
<td>6 Secreting lesion(s)</td>
<td>-0.20 (0.16)</td>
<td>1.28</td>
<td>1.7</td>
</tr>
<tr>
<td>7 Patient bothered by the appearance of the lesion(s)</td>
<td>-0.021 (0.14)</td>
<td>1.11</td>
<td>0.8</td>
</tr>
<tr>
<td>8 Others bothered by the appearance of the lesion(s)</td>
<td>1.07 (0.18)</td>
<td>1.22</td>
<td>1.2</td>
</tr>
<tr>
<td>9 Mobility limitation</td>
<td>1.02 (0.17)</td>
<td>1.09</td>
<td>0.6</td>
</tr>
<tr>
<td>10 Disgusting to the patient</td>
<td>-0.61 (0.12)</td>
<td>1.04</td>
<td>0.4</td>
</tr>
<tr>
<td>11 Disgusting to the others</td>
<td>-0.72 (0.13)</td>
<td>1.15</td>
<td>1.1</td>
</tr>
<tr>
<td>12 Fear of transmitting to the others</td>
<td>-0.68 (0.12)</td>
<td>1.31</td>
<td>2.3</td>
</tr>
<tr>
<td>13 Fear of extension to other parts of the body</td>
<td>-0.85 (0.12)</td>
<td>1.42</td>
<td>3.1</td>
</tr>
<tr>
<td>14 Worried for treatment pain/adverse effects</td>
<td>-0.73 (0.13)</td>
<td>1.26</td>
<td>1.9</td>
</tr>
<tr>
<td>15 Be frightened by the lesion(s)</td>
<td>-0.69 (0.13)</td>
<td>0.92</td>
<td>-0.5</td>
</tr>
<tr>
<td>16 Be disturbed by the lesion(s)</td>
<td>-1.47 (0.14)</td>
<td>0.82</td>
<td>-1.5</td>
</tr>
<tr>
<td>17 Frustrated by the lesion(s)</td>
<td>-0.93 (0.12)</td>
<td>0.93</td>
<td>-0.5</td>
</tr>
<tr>
<td>18 Ashamed because of the lesion(s)</td>
<td>-0.03 (0.13)</td>
<td>0.82</td>
<td>-1.2</td>
</tr>
<tr>
<td>19 Being humiliated</td>
<td>0.41 (0.15)</td>
<td>0.73</td>
<td>-1.6</td>
</tr>
<tr>
<td>20 Being stigmatized</td>
<td>0.46 (0.15)</td>
<td>0.92</td>
<td>-0.4</td>
</tr>
<tr>
<td>21 Self-isolation</td>
<td>0.79 (0.16)</td>
<td>0.75</td>
<td>-1.4</td>
</tr>
<tr>
<td>22 Influence on relationships with 1st degree relatives</td>
<td>0.71 (0.17)</td>
<td>0.82</td>
<td>-0.8</td>
</tr>
</tbody>
</table>
Table 9. (Cont’d).

<table>
<thead>
<tr>
<th>Item</th>
<th>Difficulty Measure (SE)</th>
<th>Infit MnSq</th>
<th>Outfit MnSq</th>
<th>Outfit T</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Influence on relationships with 2nd degree relatives and friends</td>
<td>0.77 (0.18)</td>
<td>0.81 -0.7</td>
<td>0.77 -0.4</td>
</tr>
<tr>
<td>24</td>
<td>Influence on relationships with colleagues/classmates</td>
<td>0.76 (0.17)</td>
<td>0.71 -1.3</td>
<td>0.43 -1.4</td>
</tr>
<tr>
<td>25</td>
<td>Interference with daily activities</td>
<td>0.07 (0.14)</td>
<td>0.95 -0.3</td>
<td>0.83 -0.7</td>
</tr>
<tr>
<td>26</td>
<td>Interference with leisure activities</td>
<td>0.72 (0.17)</td>
<td>1.04 0.3</td>
<td>0.88 -0.4</td>
</tr>
<tr>
<td>27</td>
<td>Sleep disturbance</td>
<td>0.10 (0.14)</td>
<td>1.11 0.7</td>
<td>1.00 0.1</td>
</tr>
<tr>
<td>28</td>
<td>Influence on job/study performance</td>
<td>0.21 (0.15)</td>
<td>1.01 0.1</td>
<td>0.82 -0.5</td>
</tr>
<tr>
<td>29</td>
<td>Changed travel plans to endemic areas</td>
<td>0.14 (0.14)</td>
<td>1.21 1.4</td>
<td>1.77 2.8</td>
</tr>
<tr>
<td>30</td>
<td>Changed decisions on having or going to parties</td>
<td>0.60 (0.16)</td>
<td>0.76 -1.3</td>
<td>0.57 -1.4</td>
</tr>
<tr>
<td>31</td>
<td>Reduced income</td>
<td>0.59 (0.17)</td>
<td>0.95 -0.2</td>
<td>0.80 -0.4</td>
</tr>
<tr>
<td>32</td>
<td>Increased expenditures</td>
<td>-0.15 (0.14)</td>
<td>1.17 1.2</td>
<td>1.15 0.9</td>
</tr>
<tr>
<td>33</td>
<td>Worried because of treatment costs</td>
<td>-0.89 (0.12)</td>
<td>1.06 0.5</td>
<td>1.09 0.6</td>
</tr>
<tr>
<td>34</td>
<td>Affected mental health status</td>
<td>-0.09 (0.13)</td>
<td>0.78 -1.8</td>
<td>0.72 -1.6</td>
</tr>
<tr>
<td>35</td>
<td>Feeling sad</td>
<td>-0.09 (0.13)</td>
<td>0.71 -2.4</td>
<td>0.61 -2.5</td>
</tr>
<tr>
<td>36</td>
<td>Feeling depressed</td>
<td>0.08 (0.13)</td>
<td>0.80 -1.3</td>
<td>0.62 -1.4</td>
</tr>
<tr>
<td>37</td>
<td>Feeling angry</td>
<td>0.34 (0.15)</td>
<td>0.77 -1.7</td>
<td>0.66 -1.9</td>
</tr>
<tr>
<td>38</td>
<td>Feeling irritated</td>
<td>0.39 (0.15)</td>
<td>0.74 -1.6</td>
<td>0.65 -1.6</td>
</tr>
<tr>
<td>39</td>
<td>Feeling anxious</td>
<td>-0.77 (0.13)</td>
<td>0.76 -2.0</td>
<td>0.71 -2.2</td>
</tr>
<tr>
<td>40</td>
<td>Feeling uncertain about healing/progression of the lesion(s)</td>
<td>-0.40 (0.14)</td>
<td>0.99 0.0</td>
<td>0.95 -0.3</td>
</tr>
<tr>
<td>41</td>
<td>Influence on wearing clothes</td>
<td>0.00 (0.14)</td>
<td>1.20 1.4</td>
<td>1.04 0.3</td>
</tr>
<tr>
<td>42</td>
<td>Influence on personal hygiene</td>
<td>0.28 (0.15)</td>
<td>1.09 0.7</td>
<td>1.07 0.5</td>
</tr>
<tr>
<td>43</td>
<td>Influence on practicing religious duties</td>
<td>-0.35 (0.12)</td>
<td>1.33 2.2</td>
<td>1.40 1.7</td>
</tr>
<tr>
<td>44</td>
<td>Having to do disliked activities</td>
<td>0.23 (0.14)</td>
<td>1.00 0.1</td>
<td>1.12 0.6</td>
</tr>
<tr>
<td>45</td>
<td>Preventing to do certain liked activities</td>
<td>0.03 (0.14)</td>
<td>0.77 -1.5</td>
<td>0.66 -1.5</td>
</tr>
<tr>
<td>46</td>
<td>Resulting in unfair situation which has to be tolerated</td>
<td>0.40 (0.16)</td>
<td>0.97 -0.1</td>
<td>0.84 -0.4</td>
</tr>
<tr>
<td>47</td>
<td>Causing mental preoccupation</td>
<td>-0.80 (0.13)</td>
<td>0.86 -1.1</td>
<td>0.84 -1.2</td>
</tr>
<tr>
<td>48</td>
<td>Regretting travel to where CL was common</td>
<td>-0.47 (0.12)</td>
<td>1.07 0.6</td>
<td>1.25 1.2</td>
</tr>
<tr>
<td>49</td>
<td>Reduced self-esteem</td>
<td>0.10 (0.14)</td>
<td>1.01 0.1</td>
<td>0.77 -0.8</td>
</tr>
<tr>
<td>50</td>
<td>Time wastage</td>
<td>-0.32 (0.13)</td>
<td>1.29 2.2</td>
<td>1.34 1.8</td>
</tr>
</tbody>
</table>

SE, standard error; MnSq, mean square, *: z standardized t

Table 9 showed several misfit items which could affect the measuring properties of the instrument. The person-item histogram of this preliminary version of the instrument are in Figure 13, indicating that that version of the instrument was not suitable for evaluating QoL in the sample it was administered to. It is evident from the mean item difficulty of
-1.35 logits compared to the expected mean=0.00 logits for this measure and disproportionate piling up of most question in front of those with more impaired QoL. In addition, items 8, 26, and 31 showed disordered category thresholds (Table 11), which was another problem of this version of instrument. Another significant problem associated with this P-CL-QoL was skewed distribution of choosing response categories for most items (data not shown).

Figure 13. Person-item histogram of the P-CL-QoL indicating its significant inappropriateness of in measuring QoL in CL patients.

Table 10. Items with category threshold disorders in P-CL-QoL.

<table>
<thead>
<tr>
<th>ENTRY NUMBER</th>
<th>DATA CODE</th>
<th>SCORE VALUE</th>
<th>DATA COUNT</th>
<th>% AVERAGE ABILITY MEAN MIN SQ CORR. ITEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 H 1</td>
<td>0</td>
<td>76 71</td>
<td>1.63 .13</td>
<td>.12 .9 .49 Q8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24 22</td>
<td>- .75 .15</td>
<td>.7 .29</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6 6</td>
<td>-.31 .42</td>
<td>1.4 .23</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 1</td>
<td>-.56#</td>
<td>2.7 .07</td>
</tr>
<tr>
<td>26 u 1</td>
<td>0</td>
<td>69 64</td>
<td>-1.78 .12</td>
<td>.9 .52 Q26</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>30 28</td>
<td>-.66 .17</td>
<td>.7 .39</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6 6</td>
<td>-.17 .27</td>
<td>.7 .26</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 2</td>
<td>-.32#</td>
<td>1.8 .13</td>
</tr>
<tr>
<td>31 L 1</td>
<td>0</td>
<td>82 77</td>
<td>-1.64 .11</td>
<td>1.9 .48 Q31</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>17 16</td>
<td>-.59 .17</td>
<td>.5 .39</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4 4</td>
<td>-.63#</td>
<td>.38 1.5 .13</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4 4</td>
<td>.73 .41</td>
<td>.9 .37</td>
</tr>
</tbody>
</table>

The data gathered using P-CL-QoL administration did not fit to the Rasch model (Log-likelihood Chi^2 = 9520.20, degree of freedom [d.f.] = 5192, P<0.0001). These findings

43
suggested that the P-CL-QoL should be improved and refined to be considered for measuring QoL in CL patients.

6.3.2. Improving and Refining the P-CL-QoL and Interim Instruments

To improve the measurement properties and developing an instrument that fit to the Rasch model following steps were taken: i) targeting analysis, ii) person-fit analysis, iii) category and threshold order analysis, iv) items-fit analysis, and v) differential item functioning (DIF) analysis. Criteria for diagnosis of underfit and overfit were fit MnSq>1.5 and MnSq<0.5, respectively. DIF definition criteria were: i) a |DIF contrast|>0.5 logit, and ii) a Mantel-Haentszel $P<0.05$. Refinement of the instrument was achieved though item reduction by removing the items with category threshold disorder (3), misfit (8) and items with DIF (19) from the questionnaire. The final P-CL-QoL version had 20 items, but still did not fit to the Rasch model ($P<0.0001$).

As already was mentioned, one of the main problems of P-CL-QoL was that most patients had chosen third (a lot) and particularly fourth (very much) response categories much less frequent than the first (not at all) and second (a little) response categories. As a rule of thumb, 10 observations in each category is the minimum acceptable number to have proper estimations for the Rasch model statistics [134]. To overcome this problem, we decided to merge the last two category responses and make a three-point Likert scale version of the instrument with category responses of “not at all”, “a little”, and “a lot”. The new three-category instrument showed some improvement in comparison with P-CL-QoL. Its targeting (Figure 14) got better and no category threshold disordering was observed.

Figure 14. Person-item histogram of the three-point Likert scale version of the instrument. Comparing to Figure 13, improvement in targeting and better distribution of items versus persons. However, gaps and less than optimal number of proper items for assessing persons with less QoL impairment is seen.
Despite those improvements, it did not fit the Rasch model ($P<0.0001$) so far. Like what was done with regard to P-CL-QoL, the steps were taken to improve the measurement properties of this version of the instrument. Misfit items (5) and those with DIF (14) were removed resulted in a final three-point Likert scale version of QoL instrument with 31 items. While there were significant improvement of the measuring properties of the final three-category version of the instrument in comparison with the earlier versions, it did not fit to the Rasch model ($P<0.0001$) too.

### 6.3.3 Development of CL-QoL for Measuring QoL in Patients with CL

After reviewing the frequency of the responses to different categories in the final three-category instrument, the problem of small frequencies in the last category was noticed. At this stage, we decided to combine the last two categories one more time and make an instrument with dichotomous response options of “Yes” and “No”. This version fitted the Rasch model (log-likelihood Chi$^2$=4997.83, d.f.=5194, $P=0.9740$). Person-item histogram of unrefined version of the instrument with dichotomized response options have been presented in Figure 15.

**Figure 15.** Person-item histogram of the first version of the instrument with dichotomized “Yes” or “No” choices. It shows perfect targeting and better distribution of items versus persons in comparison with previous version, however, gaps and under-coverage of persons with less impaired QoL still exists.

Then the improving steps were taken and after removing the misfit items (7) and the items with DIF (9) the final product, Cutaneous Leishmaniasis Quality of Life instrument (CL-QoL), was developed which had 34 items and showed perfect fitting to the Rasch model (log-likelihood Chi$^2$=2242.50, d.f.=2640, $P=1.000$). Figure 16 shows the person-item histogram of CL-QoL, indication very good targeting and more proper distribution of the items versus persons in comparison with earlier versions. Only one gap existed and few patients at both end of the QoL spectrum are not covered by the items.
Figure 16. Person-item histogram of CL-QoL. Very good targeting (-0.21 logits) and a relatively proper distribution of items versus persons is evident.

The Rasch model characteristics of CL-QoL are summarized in Table 11.

Table 11. Summary of the Rasch model characteristics of CL-QoL.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quantitative expression</th>
<th>Qualitative assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item Model Fit Mean-Square Range Extremes</td>
<td>0.19-1.48</td>
<td>Fair</td>
</tr>
<tr>
<td>Person Separation</td>
<td>3.10-3.18</td>
<td>Good</td>
</tr>
<tr>
<td>Item Separation</td>
<td>4.84-5.03</td>
<td>Very Good</td>
</tr>
<tr>
<td>Item Measurement Reliability</td>
<td>0.96</td>
<td>Excellent</td>
</tr>
<tr>
<td>Person Measurement Reliability</td>
<td>0.91</td>
<td>Very Good</td>
</tr>
<tr>
<td>Cronbach's α†</td>
<td>0.94</td>
<td>Very Good</td>
</tr>
<tr>
<td>Ceiling Effect: % Maximum Extreme Scores</td>
<td>3.4</td>
<td>Fair</td>
</tr>
<tr>
<td>Floor Effect: % Minimum Extreme Scores</td>
<td>4.5</td>
<td>Fair</td>
</tr>
</tbody>
</table>

*Based on Fisher’s criteria [135], † Person raw score "test" reliability.
Results of the conducted Rasch principal component analysis of the residues (PCAR) on CL-QoL are presented in Figure 17.

The Rasch PCAR, demonstrated that the raw empirical variance explained by the measures was 46.5% of the total variance, considered by most Rasch experts as poor. However, it was very close to the Rasch-modeled variance (46.9%), indicating that the data conform to the Rasch model. Figure 17 also showed that after removing the variance explained by the Rasch model three contrasts with eigenvalues larger than two existed.

6.3.4. Matching to Raw Scores and Establishing Cut Points

For the sake of simplicity, the Rasch estimated measures (logits), were transformed to a 0-34 scale, the same range of the raw scores. To match the measures to raw scores, the commands UMEAN=17.4478 and USCALE=2.8675 in Winsteps® software were used.
Raw score-measure ogive for the CL-QoL after matching logits to raw scores is demonstrated in Figure 18.

![Figure 18. Raw score-measure ogive of CL-QoL.](image)

For creating a meaningful clinical outcome out of the continuous measure, cut points had to be established. A method reported by Wright [136] was used to detect distinct levels of performance, i.e., groups of patients with homogeneous scores, which resulted in five distinctive categories of the impact of CL on QoL which were labelled: “none to minimal”, “low”, “moderate”, “high”, and “very high”.

6.4. Assessment of Impact of CL on QoL (Paper III)

The impact of CL on the patients’ QoL is demonstrated in Figure 19. According to our findings, 82.8 % of the patients who suffered from active CL lesions experienced some degrees of QoL impairment. The most observed level of impairment was “moderate” which was experienced by 28 (32.2%) patients. The second most common impact category was “low”, which was detected in 22 (25.3%) patients. Scores of only 12 patients indicated that their QoL was impaired “very high”.

Impact of CL on QoL of patient were not associated with age, gender, duration of the lesions, or severity of disease. Having low, middle, or high socio-economic status (SES) was not associated with QoL impairment (Paper III).
**Figure 19.** Impact of the QoL on patients with cutaneous leishmaniasis.
7. Discussion

7.1. Overall Methodological Points

The main aim of this PhD thesis was to develop a disease-specific instrument for measuring the impact of the disease on QoL of the patients suffering from acute CL in Iran.

The first study showed that no PRO was used as an outcome measure [25] in CL trials. The PhD student’s personal experience through encountering CL cases in different parts of Iran [80, 81, 87, 91, 137-140], indicated that there might be some concerns among patients that were not addressed by the healthcare providers. These issues suggested that a qualitative study for getting CL patients’ perspectives was paramount. Conducting a qualitative study was also an important step towards developing a disease-specific instrument for measurement of QoL in patients with CL according to a needs-based approach [141]. After CL patients’ perspectives about their disease were explored in our second study, it became possible to launch the third study, i.e., development CL-QoL, which could be used as a PRO measure in CL patients.

In 2017, Apfelbacher and Nelson in an Editorial in the British Journal of Dermatology, thoughtfully discussed the importance of having authentic PROs in dermatology and suggested a process for development and validation of PRO measures in dermatology [141]. Referring to Lasch et al. and Brod et al., they elaborated on the complexity of developing a valid PRO and the need of using robust mixed-methods, i.e., qualitative and quantitative research to achieve it [141-143]. Ten years earlier than Apfelbacher and Nelson’s publication [141], the protocol of this PhD study was developed [22]. The need for a mixed-methods approach to develop a disease-specific instrument for measuring QoL of patients suffering from CL was inspired by the works of Dovard et al., McKenna et al., Chen et al., and Whalley et al. [39, 43, 49, 144, 145]. Table 12 compares the research methods used in this thesis with Apfelbacher and Nelson’s suggested process.

Table 12. Comparison of the present study process to Apfelbacher and Nelson’s suggested process.
Table 12. (Continued).

<table>
<thead>
<tr>
<th>Apfelbacher and Nelson’s Suggested Steps</th>
<th>Steps Taken in This Project</th>
<th>Relevant Part</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conducting psychometric validation study</td>
<td>Psychometric validation study</td>
<td>Paper III</td>
</tr>
<tr>
<td>Refining preliminary measurement instrument based on findings from psychometric validation and developing the final measurement instrument</td>
<td>Developing CL-QoL from P-CL-QoL</td>
<td>Paper III</td>
</tr>
</tbody>
</table>

P-CL-QoL, Preliminary Cutaneous Leishmaniasis Quality of Life instrument. CL-QoL, Cutaneous Leishmaniasis Quality of Life instrument.

7.2. Overlooking PROs in CL RCTs

Skin disease may have a significant impact on patients’ QoL and this impact varies from one patient to another one because of their different perspectives, personal preferences, and levels of social interactions. According to a UK study, a QoL instrument, DLQI in particular, was used in 28.8% of consultations in dermatology practice [146]. This low rate of using QoL instruments may be explained by physicians’ approach to understand the impact of the disease on their patients, i.e. they assume that they know how a patient’s QoL is affected because they are experienced with many patients with same condition [146, 147]. I would like to provide a quotation from Professor Andrew Finlay, a pioneer of QoL in dermatology, whose name is associated with development of the most widely dermatology-specific QoL, DLQI:

“Although dermatologists think we have insight into the patient’s perspective, in reality, we are not that good at understanding it.” [148]

Interestingly and in support of what Professor Finlay stated, in 57.8% of consultations that DLQI was used, the results of its administration affected the health-care provider’s approach to patient’s management [146].

A systematic review conducted on all RCTs published from 2002 to 2008 in English-language databases indicated that in 25.4% of the recruited 794 studies a HRQoL were reported in the main article while another 14% reported them in their supplementary materials [149]. A systematic review on eczema RCTs published between 2000 and 2014 showed that at least one PRO was included in 93% of the 303 included studies [150].

Findings of a recent systematic review of the therapeutic RCTs in AOWCL showed that there was no change with regard to this issue [27]. In this study 89 RCTs were included, of which 40 studies were new in comparison with Gonzalez et al. 2008 review [72]. None of the 89 included studies measured QoL as an outcome. No study also measure degree of functional or aesthetic impairment, although preventing of scarring was measured in eight studies [27].
Another systematic review on treatment of CL due to *L. aethiopica* showed the same findings regarding lack of including QoL or any other PRO in the patient evaluations in the 27 included studies [151].

This lack of PROs was also reported in a systematic review of 38 RCTs on the treatment of NWCL and none of the included RCTs reported a PRO including QoL [152].

Considering underusing the PRO measures such as QoL in dermatology practice in a developed country like the UK in the 21st century [142], it is not surprising that such outcomes was not be the concern of researchers who conducted clinical studies on CL in developing countries [25, 27, 72, 151, 152]. However, the contrast between the finding of Heinl *et al.* study regarding using PROs in RCTs on eczema and the use of such outcomes in CL RCTs is dramatic [27, 72, 150-152].

According to my personal experience [80, 81, 87, 91, 137-140], the reasons behind the dramatic lack of attention to patients’ QoL in CL research could be explained by: i) almost all therapeutic studies were being designed for finding out about the efficacy of a new treatment method. This issue resulted in researchers emphasizing on defining objective clinical measures such as size of the lesions, which can easily be used to show the efficacy of the an intervention; ii) lack of human resources in clinical trial sites in developing countries: in many cases the research is conducted in the same setting e.g. a clinic where other health-care services are also provided to CL patients or even to other dermatology patients. Completing Case Report Forms (CRFs) for a patient recruited in a RCT is a demanding and time consuming task. Introducing an extra-document to the investigators who do those tasks could result in significant administrator-burden which could explain why those who develop the protocols try to avoid QoL instruments; iii) considering QoL and other PRO measures as “luxury” and “unnecessary” outcome measures. This may happen because the research team and those who developed the protocol were not aware of the important role of QoL as an outcome which could affect their new treatment method in future real life practice; and iv) considering the lack of a suitable QoL instrument which can be used to measure CL patients QoL properly.

Gonzalez *et al.* suggested QoL as a secondary outcome to be measured in studies on treatment of CL [153]. Olliaro *et al.* recommended that the main efficacy endpoint should be ulcer surface area, whenever it is possible to measure. They included the degree of scarring as one of the five parameters that ideally should be combined to define an accurate clinical outcome [154]. They considered the degree of scarring as a proxy for patient’s QoL in clinical trials assessing CL treatments, ignoring the impact of acute CL lesions on the patient’s QoL. They also stated that because of more attention to PROs in recent years, research for properly constructed PROs should be encouraged [154]. However, in a recently published article on harmonization for clinical trials methodologies on LCL, there was no proper suggestion for including a PRO as a secondary or tertiary outcome for patient evaluation during the active phase of the disease. They only considered “presence and grading of the scars” as “other efficacy parameter: stigma and cosmetic” [155]. Scar formation is a complication of LCL and is seen in some patients after their disease heal [1, 21].

Initiatives and establishment of groups such as the International Dermatology Outcome Measures (IDEOM), which started to work on psoriasis as the first disease they would
develop an outcome measure for its all stakeholders promises properly constructed outcome measures which would be relevant to patient-concerned issues in dermatology [156], however, the it might not be pertinent to CL which is an infectious disease and most commonly affect people living in developing countries.

7.3. Suffering from CL: Qualitative Approach to Experienced Problems

Findings of Paper II suggested that CL patients’ experiences could be roughly classified into two broad overlapping categories: personal and social, both caused by physical and/or emotional problems of the disease. The most important finding was that CL caused some concerns for the patients that were not reflected in the outcome assessment and not addressed in routine practice. Because of clinical characteristics of CL lesions, its association with physical problems and consequently limitations are quite expectable and understandable. Also, direct physical issues such as signs and symptoms of the lesions e.g. pain or itching were commonly discussed and managed by the health care providers. These concerns were beyond the clinical problems caused by the disease and could affect different aspects of the lives of the patients, most importantly psychosocial ones including stigmatization.

When this PhD study started, the only paper, that was retrievable from electronic databases such as Medline (via PubMed) and ISI Web of Science, in which qualitative methods had been used for studying the impact of CL on patients, was Reithinger et al.’s mixed quantitative-qualitative study [60]. Another publication was found in so-called grey literature, in which qualitative research methods were used to study the social and psychological consequences of CL [157]. They were both conducted in Kabul, Afghanistan. A recent review reported that between the publication of the aforementioned papers and September 1, 2017, four more qualitative papers studying CL patients have been published [158]. One of those papers studied stigma associated with CL scars, but not active disease, through a cross-sectional survey with an open-ended question about psychosocial impacts of CL scars [159]. Two other studies did not use any proper qualitative research methodology [160, 161]. Ramdas et al. [162], was the only article that dealt with patients suffering active CL lesions using a methodology they described as “survey-type research and qualitative ethnographic inquiries”.

Paper II showed an adverse impact of CL on mental health starting with confusion and fear of the disease and continued with anxiousness, sadness, and depression. One of the reasons for experiencing anxiety and depression was that many patients mistook their CL lesions with other diseases, including notorious infections such as leprosy and HIV/AIDS, and serious diseases like malignant tumors. These findings were similar to those of Reithinger et al., Reyburn et al., and Al-Kamel [60, 157, 161]. These misinterpretations of symptoms and signs were more common among patients who had no past experience of CL or enough information about the disease. Worrying about the consequences of CL, especially scar formation, was a concern among the participants in the qualitative study (Paper II). This was similar to Yanik et al. results which showed significantly higher levels of anxiety and depression in CL patients than healthy controls [59].

According to the findings of Paper II, stigmatization was the main social problem associated with CL. Out of the four themes that emerged from the qualitative content analysis “taking on the blame” and “struggling to cope” were most closely related to
stigma. Nevertheless, “longing for being heard and seen” also reflected some stigma-related issues, mainly because several participants considered the overall lack of knowledge in the communities where they lived and in some instances among healthcare providers as a contributing factor to the CL-associated stigma. Reyburn et al. reported the lack of knowledge as one of the two main reasons for stigmatization of CL patients, although they did not report healthcare providers’ insufficient knowledge as a problem [157].

Considering Van Barkel’s classification of health-related stigma [163], CL patients, interviewed in the qualitative study of this thesis, experienced different types of stigma. Participants with moderate or severe disease narrated that they were rejected, felt isolated or found themselves excluded, which could be considered as examples of enacted stigma. These experiences were similar to what Reightinger et al. and Reyburn et al. have reported [60, 157]. It was also demonstrated that to cope with this kind of stigma, the patients most commonly hid their lesions or in some cases, told lies about their disease. When they talked about their experiences, some also referred to other persons who had CL and had experienced discrimination. Such experiences indicated the existence of perceived (felt) stigma in that they were afraid of being treated like those whom they had heard about. Their stigma-management strategies included modifying social interactions, dismissing attitudes and behaviors of others, isolating themselves or hiding affected body parts. Examples of internalized (self) stigma were also found in the interviews with CL patients when they described how they regretted own acts (i.e. guilt) or reacted with self-disgust, and sadness. Patients with internalized stigma used the same management strategies described for those with perceived stigma.

While Reithinger et al. and Reyburn et al. used well-known stigma types which made comparing their findings to other studies straightforward, the other papers published about stigma in CL used different classifications in regard to stigma types [60, 157-161]. Bennis et al. defined a conceptual model for stigma based on Bos et al. [164] and Pryor et al. [165], which consisted of four categories: public or social stigma, self-stigma, stigma by association, and structural stigma [159]. Al-Kamel identified three CL-associated stigmas: CL social stigma, CL aesthetic stigma (CLAS), which itself had two subtypes of individual (perceived) CLAS and social (enacted) CLAS, and CL psychological stigma, apparently without any conceptual basis and consideration of accepted definitions of stigma [161]. Ramdas et al. [162], defined "aesthetic" or "unaesthetic" stigma, which was caused by visible marks or visible deformities and had significant overlap with the three types of Van Barkel’s classification [163], namely: enacted, felt (perceived), and internalized (self) stigmas, and most likely did not represent a unique entity. In brief, it seems that with the exception of Ramdas et al. study [162], the other studies showed that different types of stigma, including enacted, felt (perceived), and internalized (self) were experienced by CL patients [60, 157-61]. Ramdas et al. conclusion was that the negative reactions patients with CL receive from others might not be defined as “stigmatizing” because of the lack of Goffman's initial qualification of a ‘spoiled identity’ and its dramatic consequences [162].

As mentioned earlier, Reyburn et al. identified two sources for stigmatization in CL: knowledge-based and prejudice-based, and considered that knowledge-based stigma should be less frequent in endemic areas, where people were familiar with CL, resulting
in an overall reduction of stigmatization of CL patients in those areas [157]. They also showed that stigmatization of CL was less observed in families with past history of CL [157]. However, the results of Paper II showed that in Kashan, a known endemic area for CL in Iran, with residents who are expected to be familiar with CL and have a better understanding of patients’ situation, patients actually suffered from stigmatization and felt the expected understanding was not reflected in the behavior of their fellow Kashanis. The situation was the same in Damghan, another CL endemic region, where residents had enough knowledge about the disease, but still stigmatized CL patients. While the interviewees still attributed such experiences to lack of knowledge about CL in the community, it could also be explained by a second source for CL-stigma described by Reyburn et al., i.e., prejudice-based stigma, i.e. prejudicing a patient’s condition because of disgust and through wrong associations of his/her condition with poverty and dirtiness [157].

This finding was similar to Reithinger et al. [60] results, which indicated that while people in endemic areas for CL like Kabul, Afghanistan had an acceptable knowledge about several aspects of the disease, their behavior towards CL patients were not in line with what they know. Nevertheless, Reyburn et al. who conducted their study a few years earlier than Reithinger et al., in Kabul considered it as a relatively new endemic area where people might not have enough information about CL [157].

While individual strategies to manage CL-associated stigma have already been discussed, there are also cultural strategies, common in some endemic countries, that have to be mentioned [166, 167]. Gruel et al. [166] reported that older people who were accustomed to CL scars called it "a beauty scar" to increase the tolerability and normalization to counteract CL stigma, although this strategy was not always successful and the younger generations did not accept CL disfigurement and scars, and considered it as a life-long stigma. Desjeux [167], also reported that CL was known as ‘little sister’ in some endemic countries and became part of normal life just like a family member. Some misbelieves might result in failure to build cultural-strategies, which might explain the observed severe stigmatization of CL patients in some endemic areas such as Kabul, Afghanistan, where the disease was very common and the people were knowledgeable about it [60].

Paper II indicated that the burden of psychosocial impact of CL was larger than its physical impact. Regretting own acts and reacting with self-disgust could contribute not only to sadness and depression, but also to low self-esteem and social disconnection caused by stigmatization. While this finding was similar to other publications [60, 157-161], it seemed that CL stigma and its social impact in Iran was not as large as it was in Afghanistan, Yemen, and Morocco. Bennis et al. discussed the CL scar-associated stigma in details which was not pertinent to the findings of the present study [159].

It should also be noted that the impact of stigma in a neglected tropical disease like CL might not be reflected in a quantitative indicator of disease burden like disability adjusted life year (DALY) [75].

Reyburn et al. [157] discussed the economic problems imposed by the CL on the patients and their families, in particular, if the patient was a breadwinner man. Desjeux [168], described how CL could result in economic problems at personal and social levels and even interfere with developing agricultural and industrial infrastructures because of
depletion of labor force. Bennis et al. and Kassi et al. just mentioned economic problem as one of the social problems that were associated with CL [159, 160]. The participants in the qualitative study of this thesis revealed that depending on the location and severity of CL lesions, it could result in physical limitations for the patients, consequently affecting their income, because they could not work.

Similar to Reithinger et al. [60] and Reyburn et al. [157], the participants in the qualitative study (Paper II) sought medical care from health professionals despite being aware of the self-limiting and non-life-threatening nature of CL. Some patients found their encounters with healthcare providers were not satisfactory. The main reasons included misdiagnosis, being overlooked in making decision about their treatment preferences, and being discriminated. The results also showed that almost all the interviewed patients knew about the side effects of the standard CL treatment and even a few of them experienced some complications. However, their decision to receive the recommended treatment was not affected by fearing of or experiencing the complications. Even if several participants were aware about traditional methods of CL treatment, they preferred to be treated by medical doctors.

The participants in the qualitative study (Paper II) gave some important suggestions for improving the situation for patients with CL. They asked for:

- Increasing public awareness about CL and its psychosocial impacts including its associated stigma. The participants emphasized on the potential role of mass media especially Islamic Republic of Iran Broadcasting (IRIB) to reach the illiterates, which they considered important for achieving this goal,

- Promoting healthcare professionals’ knowledge about CL by providing better training to them by Ministry of Health and Medical Education, and

- Implementing effective preventive methods.

In summary, the findings from Paper II support the results of other publications on psychosocial impact of CL, and demonstrates clearly that CL is not a minor health problem in endemic areas and that effective educational, control, and management programs have to be developed and implemented by the organizations directly responsible for healthcare as well as other related sectors [60, 157-161, 169].

It is interesting that recently and several years after starting this PhD project, other researchers have become interested in conducting qualitative studies to capture and explore experiences of the patients who suffer from CL in endemic regions and include QoL of CL patients into future studies through an international qualitative study, coordinated and supported by Special Programme for Research & Training in Tropical Diseases (TDR) in collaboration with Drugs for Neglected Diseases initiative (DNDi) [170]. According to the published protocol of that study, individual in-depth semi-structured interviews is the planned data collection method and a maximum variation sampling approach as a variation of purposive sampling is the sampling method. They planned to interview with 10 patients of 18 years of age or older in each study site, close to the 12 patients that were interviewed in Paper II. They also planned to use thematic content analysis [170], mirroring the research methods used in the qualitative study of this PhD thesis, indicating that the methodology of Paper II was sound and appropriate.
However, they plan to analyze the gathered qualitative data by two researchers who will not be involved in the interviews, reasoning that because of multi-center nature of the study this part should be done centrally. Their plan to measure QoL in CL patients by using DLQI is also different from what has been done in regard to QoL measurement in CL patients in the current PhD project and will be discussed more in the next section (7.4) of this thesis.

7.4. Quantitative Approach to QoL in CL Patients: Measuring the Impact

7.4.1. CL-QoL: Comparison of the Development and Refinement Process with Other Instruments

Process of development and refinement of the final version of CL-QoL has been fully described in “Methods” and “Results” sections of this thesis as well as in Paper III. Herein, this process is briefly compared to a few studies that used the same methodology. Similar to McKenna et al. and Whalley et al. studies the development process was started by extracting as many as relevant items from the individual interviews conducted in the qualitative study of this project to make an item pool [144, 145]. The item pool consisted of 49 items and was much smaller than the original item pool containing 392 items that McKenna et al. had during development of the Psoriasis Index of Quality of Life (PSORIQoL), and was even smaller than their 61-item pool after they removed inappropriate items [144]. Whalley et al. made an original 56-item pool in the process of developing the Quality of Life Index for Atopic Dermatitis (QoLIAD) and reduced the number of items to 44 by removing the irrelevant items [145]. The original number of the items used for CL-QoL development was close to the one Whalley et al. had [144]. At the beginning, a four-point Likert scale was considered appropriate to avoid the “neutral” responses with the same response choices that the most widely used generic-dermatology QoL instrument, DLQI, had [46, 50]. Those 49 items were used to make an English questionnaire, which was later translated to Farsi, and then was send to a panel composed of Iranian CL experts from different basic science and clinical disciplines. They reviewed it, suggested few minor revisions, and asked for adding one question. After the suggested revisions were made, the face and content validity of the questionnaire was confirmed by the same panel and it was back-translated into English. This 50-question, four-point-Likert scale version was named P-CL-QoL, with “P” standing for “Preliminary”.

Construct validity of the Farsi version of P-CL-QoL was evaluated in a cross-sectional survey and the gathered data were analyzed by applying Rasch analysis, which did not fit to the Rasch model even after revisions were done to the instrument and its items reduced to 20 according to Rasch analyses results by following the steps suggested by Yazdani et al. and Nijsten et al. [51, 171, 172].

To develop a version of the instrument that fit the Rasch model, at first, the four-point Likert scale was revised to a three-point Likert scale to improve the problem caused by the very few answers provided by the participants to the fourth-category responses, which prevents proper estimations using the Rasch model [134]. Then, this three-point Likert scale instrument was refined according to the Rasch analyses results similar to what was described for P-CL-QoL [51, 171, 172]. However, the final version of the 31-item with three-point Likert scale did not fit to the Rasch model. Investigation of the distribution of responses provided to this instrument showed that the frequencies of third-category
responses were less than suggested minimum of 10 in several items [134]. To solve this problem, an instrument with dichotomized response choices of “Yes” or “No” was developed by merging the second and third response category. Rasch analyses was performed and necessary refinements were done according to the analyses results [51, 171, 172]. This instrument which had 34 items was named CL-QoL and fitted to the Rasch model.

Reviewing Yazdani et al. [51], McKenna et al. [144], Whalley et al. [145], and Nijsten et al. [171, 172] publications showed that after conducting Rasch analysis, the number of the items of the original instruments were reduced from 100 to 30 (Persian version of WHOQOL-100), 61 to 25 (PSORIQoL), 44 to 25 (QoLIAD), 29 to 17 (Skindex), and 16 to 11 (Impact of Psoriasis Questionnaire [IPSO]), respectively. Their results demonstrated that removing 16 items of 50 original items of CL-QoL after conducting Rasch analysis, was reasonable. Since appropriate item reduction decreases the burden for both questionnaire administrator and respondent, the ability of the Rasch method to reduce the number of items is one of the advantages of this model [173].

The reasons for removing the items following Rasch analysis of CL-QoL were misfit (10 items) and DIF (6 items). The most common reason for DIF was sex (2 items), age (2 items), duration of lesion (2 items) and two items each showed DIF for more than one variable (Paper III, Table 2). The reasons for removing items in Yazdani et al. study were category threshold (38 items), DIF (26 items), and misfit (6 items) [51]. To refine Skindex-29 by applying the Rasch model, Nijsten et al., reported that they removed 9 item for misfit and 3 items for DIF (one for gender DIF and two for showing both gender and age DIF) [171]. In another study, Nijsten et al., removed 3 items for threshold disorder (two of them also showed DIF for age too) and 2 items for significant DIF for age after conducting Rasch analysis on the original instrument [172]. McKenna et al. [144] and Whalley et al. [145] did not provide detailed information about using Rasch analysis to reduce the number of items of PSORIQoL and QoLIAD to 25 in their final versions.

During the development of CL-QoL, the original 4-point Likert scale was changed to a dichotomized “Yes” or “No” choice, which may raise the question of losing information. As already mentioned, in CL-QoL case, collapsing the categories eliminated the adverse effect of the skewed distributions i.e., frequencies smaller than 10, on the Rasch model measure estimations, which was caused by the fact that the participants did not find the most extreme category responses suitable for endorsing. Indeed, that transformation not only fitted the data to the Rasch model but also improved the quality of the instrument with regards to item separation, person separation, item measurement reliability, and person measurement reliability. Merging the categories after Rasch analysis is a common practice in particular when category threshold disorders are detected. For example, Nijsten et al. changed the five-category ordinal scales of the Skindex-29 and original IPSO to three-point ordinal scales to refine those instruments using the Rasch method [171, 172]. McKenna et al. and Whalley et al. both used dichotomized “Yes” or “No” choices in the final versions of the disease-specific instrument they developed and mentioned that it made their instruments practical for use [144, 145].

While a QoL instrument with 34 items may be considered too long, it should be mentioned that short questionnaires could reduce person and test reliabilities [174].
Whalley et al. reported that completion of QoLIAD, which had 25-items with dichotomized “Yes” or “No” response choices took a maximum of 5 minutes [145]. Extrapolating their finding to estimate the needed time for CL-QoL completion, made 7 to 10 minutes reasonable.

The overall structure of CL-QoL is discussed in section 7.5.

7.4.2. QoL in CL Patients: Results of Using CL-QoL

The ultimate aim of this thesis was development of a disease-specific instrument for measuring QoL in patients with CL, which was achieved by developing CL-QoL. So while the results of using CL-QoL were reported, it was not the focus of this thesis. However, evaluation of the CL impact on patients’ QoL using CL-QoL showed a few interesting findings (Paper III, Table 5), most importantly its ability to measure QoL and provide clinically meaningful categories of the CL impact on the QoL of patients suffering from acute CL and no association between QoL scores and the diseases severity, which suggested that QoL of patients with CL should be measured properly, because clinical assessment of the disease might not be enough for optimal patient care.

Previous studies that investigated CL patients QoL, used generic-dermatology QoL instruments [59, 62, 64, 65, 67-69]. DLQI was the most commonly used instrument [62, 64, 65, 67-69]. However, Turkish Quality of Life for skin diseases instrument, also known as Dermatology Quality of Life (DQL), was also used in one study [59]. Neither of those instruments was validated using modern psychometric methods such as Rasch analysis [46, 61]. DLQI’s problems regarding its lack of fundamental measurement properties including unidimensionality and invariance of measurement are well-known [70, 71]. In addition, generic dermatology QoL instruments might have some flaws by not including some salient questions about QoL in CL such as those related to the infectious nature of this disease. In addition, DLQI evaluates QoL of the patients for the last week prior to the time of its completion, while CL-QoL evaluates CL patients’ QoL over the duration of the disease up to the time of its completion.

An overview of the studies that have already been published on the measurement of QoL in CL cases with active lesions has been provided in section 2.13. of this thesis. Considering the above mentioned issues, it was not possible to have a robust comparison between the results of CL-QoL application to studies that used DLQI or DQL.

The low mean DLQI scores of patients in Vares et al. study supported the finding of the tendency of the patients to choose lower categories on the majority of items of the P-CL-QoL although Noorpisheh et al., Niforoushzadeh et al., and Khoshnood et al. studies did not support this finding [62, 64, 65, 68].

Similar to the results of CL-QoL use, Vares et al., Noorpisheh et al., and Khoshnood et al., did not find any significant difference in QoL between male and female patients [62, 64, 68].

One quantitative QoL study was found in which QoL of the family members but not the patients were investigated [175]. Handjani and Kalafi, used Persian validated version of the Family Dermatology Life Quality Index (FDLQI) to assess the impact of four skin diseases including CL on the family members of the patients [175, 176]. They
acknowledged that their sample size was small, for example only five CL patients were recruited to the study, which explained why even large differences were not detected as statistically significant. Their findings showed that the impact of CL on the family members of the patients (mean FDLQI score = 12.00 [± 4.80]) was smaller than what was observed for the other three diseases, vitiligo, psoriasis, and pemphigus vulgaris, although the difference was not statistically significant [175]. That finding might be caused by the fact that mean duration of CL was shorter (0.62 ± 0.23 [unit of time was not provided but most likely it was year]) than the other investigated diseases, although they reported that there was no correlation between duration of the disease and FDLQI scores, which was most likely due to the small sample size of the study [175]. The main complaint of the family members of the CL patients was the time they had to spend for looking after their partner or relative [175].

Erber et al. [170], have mentioned that patient’s views have not been genuinely considered so far, and particularly, outcomes affecting patients’ QoL have been rarely reported in clinical studies. They have also mentioned that they expect significant heterogeneity regarding QoL-related outcomes because of the diverse cultural contexts. However, they plan to use what they described as: “an established and internationally validated outcome measurement instrument such as the Dermatology Life Quality Index” “as a frame of reference in combination with research approaches for linking outcome measures to established instruments, for example, the International Classification of Functioning, Disability and Health Linking Rules” [170]. Their plan to measure CL patients’ QoL does not seem to be optimal, because the version of DLQI that has been widely used and they referenced to (Finlay and Khan. 1994 [46]) has several problems with regard to fundamental measurement [70, 71] and more importantly is not a disease-specific instrument which has been developed according to a needs-based model.

7.5. Qualitative and Quantitative Approaches: Comparison of Findings

Before conducting this study, the lived experiences of patients with CL were explored in a qualitative content analysis study. While there were several codes related to the symptoms and signs of CL, those codes contributed to subcategories and categories that ended up in themes that mainly represented psychological or social issues. After using the Rasch method in the psychometric evaluation study of this thesis, only one of five questions that were directly asking about CL symptoms and signs remained on the final version of the developed instrument. Other remaining items on CL-QoL were mostly related to psychological and social impacts of CL. Considering the emergence of two main themes of “taking on the blame” and “struggling to cope” that were strongly correlated to the CL-associated stigma in the qualitative content analysis study of this thesis, this finding was not unexpected.

Several remaining items asked about stigmatization, self-isolation, self-esteem, humiliation, patients relations with others, and their social limitations. Most of the items related to the effects of CL on the emotions and feelings also remained in CL-QoL. Items about the appearance of the lesion(s) and its consequences were also present in the final version of the developed instrument. These findings were in line with the results of the qualitative study, which found stigma as main problem.
In addition, results of this quantitative study of the thesis supported the overall findings of the conducted qualitative study that clinical symptoms and signs of CL did not directly affect patient’s QoL. For example, one item asking about mobility, i.e. physical limitation was removed but most items related to social and authority (decision-making) limitations remained.

Questions asked about different issues related to the treatment were also removed according to the conducted Rasch analysis. This finding was somehow different from the results of the qualitative study of the thesis in which the experiences of CL patients encountering with healthcare facilities and community contributed to the theme “longing for being seen and heard”.

One of the reasons for the apparent differences between the qualitative and quantitative findings of this thesis was that in that the aim of qualitative part was to explore the patients’ experiences using a non-random purposive sampling method for getting maximum variation of disease conditions. Gathering detailed data through in-depth interviews from the patients whom might not be frequently found in random sample of the CL patients in Iran resulted in identification of some uncommon symptoms, signs and related to CL that would not be experienced by the majority of CL patients. It would be quite likely that some of those items not be endorsed in a survey conducted on a consecutive or random sample of CL patients.

A good example to explain the above paragraph could be item # 5 of the original questionnaire: “Has/have your lesion(s) been "foul-smelling"?”, which supposed to be answered according to a four-point Likert scale: a) not at all, b) a little, c) a lot and d) very much”. While it was extracted as an item and included in the original questionnaire because one of the patients in the qualitative study experienced it, reviewing the frequency of response to it revealed that only 5 participants in the survey chose an answer other than “not at all” four chose “a little” and one chose “very much”. In other words, more than 95% of CL patients in the survey part did not find “foul-smelling lesion” as a problem. So, removing this item during refinement of the instrument and its absence in the final version of CL-QoL seemed reasonable.

Indeed, these finding supports critical importance of using mixed-method, i.e., qualitative-quantitative approach, for developing proper QoL instruments. While interviews by the patient are considered the best method for item generation to be used in a needs-based developed QoL instrument, a proper psychometric evaluation will result in a final practical questionnaire with the most suitable items and an acceptable length [141, 177].

It is important to point out that the main aim of a QoL instrument that has been developed according to the needs-based approach is to investigate the patients’ concerns about their disease which results in some “needs” that have to be fulfilled. These concerns are not usually assessed properly through sole clinical examinations and so are also known as “unmet needs”.

7.6. Implications for Patient Care and Public Health Decision Making

Miller et al. [178], findings supports the hypothesis of including PROs such as QoL in clinical research and ultimately in routine practice to address the so-called “unmet needs”
of the patients. So, one of the direct implications of the findings of this thesis is to use CL-QoL as a PRO measure to improve the current care and management of CL patients. It will help the physicians and other health care providers to get more information about “unmet needs” of the patients and address them.

Carlson et al. [179], reported that evaluating PROs in initial screening of the patients with different types of cancers regarding their distress could improve patients’ compliance and make a better communication between healthcare professionals and the patient, consequently resulted in fewer need of face to face visits because of more effective phone consultations. While CL is very different from cancers in terms of its natural course, severity, and outcomes, Carlson et al. [179] finding may be pertinent to use a needs-based developed QoL instrument like CL-QoL in CL clinics. It is likely that when CL patients notice through completing CL-QoL, that the healthcare providers are concerned about some issues that usually are not discussed during the visits, they communicate better with the healthcare team, and consequently trust them more, which may improve patients’ tolerance and compliance with regards to the recommended treatments.

In the field of dermatology, Salek et al. [146] reported that in 57.8% of consultations that DLQI was used, the results of its administration affected the health-care provider’s approach to patient’s management, which might be pertinent to administration of CL-QoL.

Beyond the development of CL-QoL, which could potentially be instrumental in improving direct management of CL patients in routine practice, the findings of this thesis revealed several other important issues that have to be improved to ameliorate the problems that CL patients encounter with in their daily lives.

The qualitative study of this PhD thesis revealed that psychosocial problems and on top of them stigma is a main issue for patients with acute CL. This is why they were expected to be heard and seen by the both ordinary people and health authorities. Participants in the qualitative study of this thesis believed that disseminating knowledge about CL in community and better training of healthcare professional could improve CL patients’ situations.

Finding of this thesis support Kassi et al.[160] recommendation of adopting a multifaceted approach by the health authorities to reduce the social burden and the associated stigma of CL. This approach should target CL itself through improving the provided care for CL patients and educating people about the disease. Developing and implementing healthcare educational and interactive de-stigmatizing programs could play important roles to improve CL patients' situation.

Effective preventive methods was an important demand of the CL patients who shared their experience about the disease. Although according to the finding of a study conducted in an endemic area in Iran, with the exception of educational programs, applying other known preventive methods such as using insect repellants, pesticides, and bed-nets were not cost-effective or cost-benefiting [180], improving garbage and sewage management is recommended.
7.7. Limitations

The first study was conducted between 2003 to 2006 and was published in 2007 as the first systematic review on the treatment of CL. For this reason, it might be considered rather outdated now. It also included only RCTs conducted on the acute Old World CL. In addition, the main goal of that paper was to critically appraise the quality of design, conduct, and report of the included studies, not evaluation of the outcomes including PROs per se. However, since its publication, several other systematic reviews on different types and aspects of CL have been published and support the findings of the first study of this thesis regarding the lack of PROs in CL studies [25, 27, 72, 151-153].

In the second study, only patients who had sought medical care for their CL lesions were recruited, so those who did not look for receiving medical treatment were not included. An expert panel had been consulted and it was agreed that it is unlikely that the experiences between the two groups were considerably different. Previous studies in Afghanistan showed that those CL patients believed that their disease required medical care [59, 157], which was taken as an indication of the same situation in Iran. It is unlikely that recruiting patients who came to CL clinics introduced any selection bias to the study.

The transferability of the results of this study is limited because only patients with acute CL, i.e., lesions duration less than 6 months, were included in it. Those who suffered from other forms of CL, including those with longer duration of active lesions and leishmaniasis recidivans, could be considerably different in terms of clinical course of their disease and had different experiences and perceptions about their disease.

Most likely, experiences of children with acute CL and their perception of their disease would be different from adult patients too. Since conducting and analyzing qualitative studies with children needed certain skills and its findings could not be merged with those of adult patients, people younger than 18 years old were not included in this study. It could be considered as a limitation since children are a large and important group at risk for getting CL in endemic areas.

Several limitations are present in the third study. First, a group of Iranians CL experts were asked to provide their feedback on the first developed questionnaire based on the findings of the qualitative study of this thesis. That questionnaire was revised according to their suggestions and they were asked to review the revised version, i.e. P-CL-QoL, which they found its face and content validity appropriate. However, that process was not done through a robust Delphi methodology.

Categorization of socio-economic status (SES) of the patients was not optimal. Because of limited resources and some contextual issues in Iran, it was not possible to do a more appropriate classification of patients according to their SES. Participants were simply asked about how they consider their own SES. So, interpretation involving this variable should be done cautiously.

Some aspects of reliability and validity such as reproducibility (repeatability) and discriminative validity were not evaluated. One of the reasons for this shortcoming was that the overall clinical changes in CL, even in case of receiving treatment, is slower in comparison with some other dermatologic conditions such as eczema. It was not possible to administer the CL-QoL to the same patients after a short interval and also many patients
with CL would not return to the healthcare facility when they find out about the self-healing benign nature of their disease. Concordant validity of CL-QoL was not evaluated because no Persian Rasch-validated dermatology-specific QoL instrument such as Skindex-17 was available. In addition, it would be difficult to interpret the findings of a concordant validity study in this study because of the different characteristics and clinical features of CL and the dermatologic conditions based on which dermatology-specific QoL instruments have been developed.

After conducting the Rasch analysis on the gathered data all but one of the questions related to the symptoms and signs of CL was removed, which may raise the questions about face and content validity of the final version of CL-QoL. All items directly related to the treatment and economic aspects of the disease were also removed, causing same concerns. However, it should be noticed that CL-QoL is supposed to measure QoL of CL patients not their disabilities and limitations or their attitudes. The goal of CL-QoL is to provide insights to “unmet” needs of the CL patients, not being substituted for clinical findings.

While the sample size of the third study was acceptable for analyses on the whole participants, it might be not large enough to detect statistical differences in subgroup analyses.
8. Concluding Remarks

Findings of the first study of this thesis showed that CL patients’ concerns about their disease was neglected in all RCTs conducted on acute Old World CL. No PRO was included in patients’ evaluations as a secondary or even tertiary outcome measure. This finding was also observed in the more recent conducted systematic reviews on CL RCTs.

Findings of the second study of this thesis showed that the lived experiences of the CL patients could be represented in four main themes: "Fearing an agonizing disease" which reflected patients' experiences of disease development, "struggling to cope" and "taking on the blame" both illustrated how patients experienced living with the disease and "longing for being seen and heard" referred to the patients' experiences with community and healthcare system. The first theme was associated with the psychological impact of CL including confusion, sadness, depression, and the resulted anguish. The second and third themes were correlated to the social problems CL patients’ encountered with, most importantly CL-associated stigma. Both felt and enacted stigma were existed and raised major social concerns. The last theme dealt with the CL patients’ expectations and demands from the health and community authorities to close the knowledge and awareness gap, which they believed was the main reason for their social situation, particularly for being stigmatized. In brief, the second study showed that psychological and social dimensions of CL were complex and impaired patients' lives by causing psychological burden due to anxiety and depression and limiting their social interactions because of stigmatization. This study also indicated that health authorities in collaboration with other relevant sectors had to plan and implement programs to increase CL awareness and to reduce its associated stigma, which would consequently improve patients' social condition. The conducted qualitative study was also the center for achieving the ultimate aim of the thesis, i.e., development of a disease specific instrument for measuring QoL in CL patients according to a needs-based model.

The main result of the third study of this PhD thesis was development of CL-QoL, which is a disease specific instrument for measuring QoL in CL patients according to a needs-based model. The final CL-QoL had 34 items with dichotomous “Yes” or “No” response choices, which fitted to the Rasch model and has fundamental measurement properties such as unidimensionality, invariance, and local independent items. It was demonstrated that CL-QoL could define five clinically meaningful different categories of the impact of CL on patients QoL. These characteristics made CL-QoL a potential suitable PRO measure for patients with acute CL in Iran. It is recommended that CL-QoL be used in future clinical studies on CL, particularly in RCTs, and in routine medical practice in Iran, to measure QoL as a secondary outcome.

It is important to mention that studies of this PhD thesis each had limitations. The first study was published in 2007 and could be considered outdated. However, as previously mentioned, more recently conducted systematic reviews, even those published in 2016 and 2017, supported its findings. The qualitative content analysis study may have limited generalizability. The findings of the third study are preliminary and CL-QoL has to be validated in other populations preferably using the Rasch method. Some aspects of its validity and reliability that were not investigated have to be evaluated.
9. Suggestions for Future Research

Children and teenagers constitute a very large group of CL patients. Both the second and third studies of this thesis were conducted on patients who were 18 years old or older. So, conducting qualitative researches with children and teenager participants in the future is recommended. In addition, it is likely that a children’s version of CL-QoL be needed to measure QoL of children and teenagers who suffer acute CL. While CL-QoL may be used as a base for development of that instrument, its development and validation process should be as robust as possible and preferably follow Apfelbacher and Nelson’s suggested process [141].

CL-QoL has the potential for being used in future researches on CL both in Iran and in other countries. As it has already mentioned with regard to limitations of its validation process, further validation studies are recommended. Cross-validation of CL-QoL with a Persian validated version of a Rasch validated generic-dermatology QoL instrument such as Skindex-17, which at the time of conducting this study did not exist is recommended. In addition, psychometric evaluation using CTT methods is suggested.

To use CL-QoL in other countries that do not speak Farsi, a validation process that included translation and back-translation, and applying the Rasch method is recommended. The main reason for recommending further Rasch validation in the other countries is to make CL-QoL valid for being used in the settings and populations where the cultural contexts are different from Iran.

While the main potential use of CL-QoL will be as a secondary outcome measure in CL clinical trials, it can also be used in other study designs such as cross-sectional surveys to measure and compare QoL in CL patients from different populations. In addition, it might be possible to use CL-QoL to quantify the burden of CL for making comparison to other diseases through cross-validation of it with instruments such as EQ-5 D, although because of certain characteristics of CL such as being self-limited and involving only skin this kind of research have to be considered cautiously [181].
Acknowledgements

First and foremost, I would like to sincerely thank God for everything I have in my life.

The first person, I would like to deeply thank is my main supervisor, Professor Berndt Stenberg. Berndt’s role has been much more than being a superb professional academic supervisor. He is my mentor and role model too. I hope that I deserve having such a wonderful luck to study and do research under his supervision. I cannot overemphasize the supporting role of Berndt when it comes to my thesis. His extensive knowledge and experience in public health, epidemiology, and medical research was helpful in each and every step of writing this thesis. His supports were not limited to the scientific issues. Berndt and his dear wife, Lena, always and extensively supported me during my several travels to Umeå. I do not know how many times you invited me to your beautiful home, or to wonderful restaurants (the number is too high!), but each and every of events are among the best times that I had over the past decade. You kindly introduced me to your wonderful sons and their families, which I really appreciate. You taught me many things about the rich culture and nature of northern Sweden by taking me to unimaginably beautiful places and wonderful cultural events from local markets to museums and movies. The lunches with you at Bokcafè Pilgatan will never be forgotten.

Dear Berndt and Lena, your kindness and supports have been beyond any imagination and I could never thank you enough. You paid attention to all aspects of my life and were always available to help me. You taught me many important lessons about how to become a better person. I hope that I could have learnt from you and use them in helping others.

I would like to thank my co-supervisors Professor Maria Emmelin and Dr. Hans Stenlund, who guided me to learn the required knowledge and skills I needed for conducting the researches contributing to this thesis too. While I was studying my PhD, Maria and her husband Andres Emmelin went to southern Sweden to continue their academic adventures at Lund University. However, she was always available and helped me with regards to all the questions I had and the assistance I needed for my PhD studies and its related papers. I had several travels to Malmö to work directly under her supervision, and also we communicate extensively via email and Skype, no need to mention that when she was in Umeå, she arranged a meeting with me despite her busy schedule. Whenever, I traveled to Malmö, she and Anders invited me to their home. They also took me to several interesting cultural events including concerts and musical shows, just to name one: “West Side Story”? Thank you Maria and Anders!

In addition, I deeply thank my local supervisor and the Director of the Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), Tehran University of Medical Sciences, Professor Alireza Firooz, for sharing his experience about cutaneous leishmaniasis, reviewing my work critically, and supporting me. I also would like to sincerely thank Professor Ingeborg Nilsson, Unit of Occupational Therapy, Department of Community Medicine and Rehabilitation, Umeå University, Umeå, Sweden, for assisting me with the Rasch method and her scientific contribution to the third paper of this thesis.

I greatly appreciate Professor Lars Weinehall, my examiner and the former Head of the Unit for his supports and assistance. His deep understanding of the situations a PhD
student might encounter and his wise advices were always useful and encouraging. My special thanks to Professor Anna-Karin Hurtig, Head of the Unit, Professor Miguel San Sebastian, Director of Studies, Research Training, and Professor Anneli Ivarsson, former Head of the unit, for their all kind considerations and assistance. Without their extraordinary support, it was not possible to continue and finish this PhD.

I would like to deeply thank Dr. Klas-Göran Sahlen and Dr. Margareta Norberg for spending their time to review my thesis and provide constructive comments and suggestions in the pre-defense session. Their suggestions helped me to improve my thesis significantly.

Special thanks to Ms. Birgitta Åström, Ms. Ulrika Harju, and Ms. Karin Johansson for their extraordinary supports and kindness, which began before commencement, continued during, and presumably would continue after the end of my studies in Umeå! Birgitta, Ulrika, and Karin helped me with every details related to obtain my visas and residence permits, travels, accommodation, insurance, participation in the courses, and all issues related to my thesis including its registration, follow-ups, submission of reports and study plan revisions, mid-term seminar, pre-defense, and defense sessions. Karin’s supports in case of obtaining entry visa for my mother to make it possible for her to be present at my defense was beyond all expectations, although my mother could not get the visa at the end. I also would like to thank Ms. Lena Mustonen, who handled the web-related administrative issues, particularly, with regards to my thesis, and Ms. Susanne Walther, who handled financial issues.

I would like to sincerely thank Mr. Göran Lönnberg for all his supports and kind considerations. Göran is one of the most intelligent friends that I have. He is also one of the kindest and most supportive persons I have ever known. During the years that I was studying my PhD, I encounter several problems with my computers. On every and each occasion, he was available and helped me with everything, from providing assistance for connecting to the Wi-Fi network and solving software issues, to installing the needed software and replacing hardware parts of my laptop! Last but not least, his comments and suggestions about proper use and maintenance of computers, were invaluable.

I acknowledge Dr. Yahya Dowlati, the Honorary Director of CRTSDL kindness from the bottom of my heart. I have no doubt that if I did not know him, I would not enter the passage to study a PhD degree. His personal and professional supports will never be forgotten. In addition, I wish to thank Professor Ali Khamesipour, Deputy-Director of Research of CRTSDL for his continuous encouragement and supports in many ways. Most of the patients’ photos used in my thesis, including the original photo used in designing the thesis cover are from his extensive collection of clinical CL photographs. I also sincerely appreciate the great assistance I received from Mrs. Akram Miramin Mohammadi, Dr. Rezvan Talae, and Dr. Nessa Aghazadeh, who were members of my research team in Iran and contributed significantly to the last two original papers of this thesis.

I am really grateful to all other faculty and staff at the Unit of Epidemiology and Global Health, Department of Public Health and Clinical Medicine, Umeå University as well as the international group of PhD students for creating a warm, encouraging and friendly study environment. I also deeply and sincerely thank the kindness of the staff and faculty
members of Dermatology and Venereology, Department of Public Health and Clinical Medicine, Umeå University who allowed me to share the space and facilities of their unit and never allowed me to feel lonely. I would like to extend my thanks to the staff of CRTSDL in Iran, particularly to Professor Mansour-Nassiri-Kashani, Executive Deputy-Director, and Mr. Seyed Ebrahim Eskandari, Executive Manager of CRTSDL.


I am aware that there were many more friends, but I could not remember they names. I hope they forgive me in this regard.

Last but not least, I wish to deeply and sincerely thank my dear mother, Mrs. Parvin Mortazavi Nejad, who have devoted her life to support me in all ways always. After my father passed away and within just a few months after that incident, she experienced a serious disease, and I imagine she needed me presence and my supports more than anytime. Instead, she supported me in all imaginable ways and encouraged me to continue my studies. Thank you my dear mother for being so nice and strong!
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Appendix I. Calculations of outfit and infit mean squares, and z-standardized t.

Calculation of outfit mean square (Outfit MnSq):

\[
U_n = \frac{\sum_{i=1}^{L} Z_{ni}^2}{L} \quad \text{and} \quad U_i = \frac{\sum_{n=1}^{N} Z_{ni}^2}{N}
\]

Calculation of infit mean square (Infit MnSq)

\[
U_n = \frac{\sum_{i=1}^{L} Z_{ni}^2 W_{ni}^2}{\sum_{i=1}^{L} W_{ni}^2} \quad \text{and} \quad U_i = \frac{\sum_{n=1}^{N} Z_{ni}^2 W_{ni}^2}{\sum_{N=1}^{N} W_{ni}^2}
\]

Calculation of z-standardized t (ZSTD):

For this calculation, Wilson-Hilferty transformation is used

\[ q^2 = \frac{2}{\text{df}}, \]

when

\[ \text{df} \approx \text{MnSq divisor} \]

\[ ZSTD = (\text{MnSq}^{1/3} - 1)(3/q) + (q/3) \]
Appendix II. Interview Guide.

Interview Guide

**Project title:** Development and Validation of a Disease-Specific Instrument for Evaluation of Quality of Life in Adult Iranian Patients with Acute Old World Cutaneous Leishmaniasis

**Document:** Thematic “Interview Guide” for Individual in-depth interviews to explore how Iranian patients *perceive, feel and experience* having acute cutaneous leishmaniasis.

**Conduction of Interview**

The interview will begin with an introduction through which the interviewer and interviewee will briefly introduce themselves to each other. The interviewer will inform the interviewee about the recording of the session as well as the confidentiality of all recorded and noted materials including future transcription. The interviewer will also appreciate the informant’s willingness to participate.

General themes for interview are as follows:

A. General questions:

1. Please describe when you first noticed that you had the skin lesion that you are now being treated for?
   a. What has happened?
   b. What do you think made you get this disease?
   c. What made you decide to seek medical help?
   d. How would you describe your health in general before you had the disease?
      i. What does it mean to be healthy?
      ii. How did your health change when you got these lesions?

B. Interference with daily activities

2. How does your disease interfere/have changed your daily life including your prayers and so on?
   a. Physical activity
   b. Travelling
   c. Taking care of children, housework, farm work, etc.?

C. Emotional aspect of the disease

3. Please describe your feelings about your disease.
4. What are your main concerns about your disease?
5. Have you experienced any change in your mood/feelings after getting this disease? Please explain them in your own terms.
6. What do you think about the outcome of your disease, about its treatment and so on? Please describe your main concerns.

C. Social aspect

7. How have people in your community reacted towards you having this disease?
   a. Family?
   b. Friends?
   c. Community members?
   d. Have you experienced being talked about in a derogatory way, which you think is associated to your conditions?
   e. Have you ever experienced being treated differently than before, due to your condition?

8. How have your own attitudes towards others changed since you got the disease?
   h. Family?
   i. Friends?
   j. Community members?

D. Economical aspect

9. Would you tell me what changes in your economy has resulted by AOWCL? Please explain how it has influenced your income and/or your expenditure?

E. Gender and class differences

10. You have now described your experience of the disease? How would you think these experiences would differ for other people
    a. Opposite gender?
    b. Belonging to another class?

F. Ending question

11. Is there anything else that you wish to add?

The interview will be ended with appreciation of the participant for providing his/her opinions and as well as spending his/her time.