

ORIGINAL ARTICLE

Clinical Allergy

Development and validation of the Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-QoL)

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Funding information

The project was cofounded by the International Institute of Dermatological Allergology (I²DEAL) at Charité—Universitätsmedizin Berlin.

Summary

Background: Cholinergic urticaria (CholU), a common form of chronic inducible urticaria, is characterized by itchy wheals that occur in response to physical exercise or passive warming. CholU patients frequently exhibit a high burden of disease. As of yet, no specific instrument is available to assess their disease-related quality-of-life (QoL) impairment.

Objective: The aim of this study was to develop and validate the first disease-specific QoL instrument for CholU patients, the Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-QoL).

Methods: Using a combined approach of the literature search, semistructured patient interviews and expert opinion, we developed 96 potential CholU-QoL items. Subsequent item selection was performed by means of impact analysis complemented by an expert review for face validity. The resulting final CholU-QoL was then tested for levels of validity, reliability and influence factors in 88 CholU patients. In parallel, an US American-Canadian English version of the CholU-QoL was developed.

Results: The final 28-item CholU-QoL was found to have a 5-domain structure ("symptoms," "functional life," "social interaction," "therapy," "emotions") with excellent internal consistency. The CholU-QoL also showed a valid total score, and good levels of convergent validity, known-groups validity, as well as test-retest reliability. Multiple regression analysis found no significant drivers of the CholU-QoL total score.

Conclusions and Clinical Relevance: The CholU-QoL is the first disease-specific QoL instrument for CholU and also the first specific QoL measure in the field of chronic inducible urticarias. It may serve as a valuable tool for clinical trials and improve routine patient management.

KEYWORDS

cholinergic urticaria, patient-reported outcome, quality of life

1 | INTRODUCTION

Cholinergic urticaria (CholU) is characterized by itchy wheal and flare-type skin reactions triggered by physical exercise or passive warming.¹ This frequent form of chronic inducible urticaria affects

up to 20% of young adults.² It usually lasts for years and frequently has a high impact on the patient's quality of life. Severely affected patients are not able to study, work or do housework.¹

As of yet, no curative therapies are available for CholU. Instead, symptomatic therapies are the mainstay of treatment. The current

guideline (EAACI/GA²LEN/WAO/EDF urticaria guideline) recommends to use H1-antihistamines in licensed dose as first-line therapy and up to 4 times the licensed dose as second-line treatment in ChIU.³ Unfortunately, in many patients, this treatment is not sufficient to achieve complete symptom control.⁴ Accordingly, ChIU patients are commonly regarded as difficult to treat (Cases or case series⁵⁻⁷), and new therapeutic options are needed.

One prerequisite for the development of new treatment options is the availability of valid and reliable outcome measures to assess treatment effects. However, as of recently, such tools for ChIU were largely missing. This might be one of the reasons why only very few randomized controlled clinical trials have been performed in ChIU. Very recently, pulse-controlled ergometry provocation testing was introduced as an objective method for the diagnosis of ChIU,⁸ and the ChIU activity score (ChIUAS) was described as the first disease-specific diary-type tool to assess disease activity.⁴ In addition to disease activity, health-related quality of life (QoL) is another important and recommended outcome measure in both routine patient care and clinical trials. Disease-specific QoL instruments such as the chronic urticaria quality-of-life questionnaire (CU-Q2oL) and the angioedema quality-of-life questionnaire (AE-QoL) have been available for chronic spontaneous urticaria for years.⁹⁻¹¹ In contrast, specific tools for chronic inducible urticaria forms, including ChIU, are still missing, although leading health authorities strongly recommend the use of patient-reported outcome tools in randomized controlled trials.^{12,13} Accordingly, we here report the development and validation of the first disease-specific health-related QoL instrument for ChIU, the Cholinergic Urticaria Quality-of-Life Questionnaire (ChIU-QoL).

2 | MATERIALS AND METHODS

This study was approved by the Ethics Committee of the Charité—Universitätsmedizin Berlin (EA 1/385/13) and Mainz (837.129.15 (9897)) and registered with the German Clinical Trials Register (DRKS-ID: S00012318). It was conducted according to the Declaration of Helsinki and the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) Guidelines, national laws and regulations at the Department of Dermatology and Allergy, Charité—Universitätsmedizin Berlin and the Department of Dermatology, University Medical Center Mainz. All patients gave signed informed consent before participating in the study. Patients were all referred to the Urticaria Center of Reference and Excellence (UCARE) by dermatologists with the suspected clinical diagnosis of ChIU. We confirmed this diagnosis based on a systematic history, in all patients, and on the presence (and/or photodocumentation provided by patients) of the clinical signs and symptoms of ChIU and/or the results of provocation testing. Cholinergic urticaria was the main diagnosis and the dominant condition in all patients. Some patients had concomitant diseases including other types of chronic urticaria.

The development of the ChIU-QoL was performed in 3 steps: (i) item generation, (ii) item selection and (iii) ChIU-QoL validation.

2.1 | Item generation

Item generation was performed in accordance with current recommendations for patient-reported outcome instrument development.¹²⁻¹⁵ In brief, a ChIU core development group (S.A., J.R., K.W.) identified specific fields of disease-related QoL impairment that should be covered by the ChIU-QoL. This group also defined the scoring system for ChIU symptoms, anchors for the evaluation of the ChIU-QoL performance and helped to design and conduct the item selection phase and the ChIU-QoL validation study.

Item generation was performed using 3 concomitant and sequential strategies: (i) a literature search for published data on QoL impairment in ChIU patients; (ii) semistructured interviews with 10 patients with a history of ChIU who were recruited at the Department of Dermatology and Allergy, Charité—Universitätsmedizin, Berlin and (iii) inclusion of ChIU expert opinion of the core development group.

Item responses were designed as 5-point Likert scales (LS)¹⁶ with the answer options "not at all"; "somewhat"; "moderately"; "much"; "very much" as well as "never," "seldom," "occasionally," "often" and "very often." The recall period of all items was chosen to be 7 days.

2.2 | Item selection

All questions identified in the item generation phase were administered to 50 ChIU patients recruited at the Department of Dermatology and Allergy, Charité—Universitätsmedizin, Berlin (36 females; mean age $\pm$ SD: 40.7 $\pm$ 15.6 years; median: 35; range 20-79). These patients were asked to complete all items and to score their relevance and importance (impact analysis, see below). Furthermore, all patients were requested to rate the understandability and comprehensibility of the generated items. Item selection was subsequently performed by means of impact analysis, complemented by the core development group of the selection for face validity.

2.3 | Impact analysis

An impact analysis was performed to exclude all items from the final ChIU-QoL with a low impact. To this end, patients were asked to rate each question regarding their importance (1 = not important to 5 = extremely important) and whether they had experienced the item content within the last year (yes/no). The "importance" and "frequency" of each item was then computed as the mean of all importance values and the proportion of patients who experienced the item content. Subsequently, the "impact score" was calculated for each item by multiplication of "frequency" and "importance." An impact score of >2.5 points was chosen as a cut-off point for the inclusion of items.

2.4 | Expert review

The impact analysis was complemented by a review of the core development group. Redundant and unprecise questions were eliminated, and a final assessment of the selected items for their face validity was performed. In addition, the recall period of the final

CholU-QoL was changed from 7 to 14 days. This was based on patient input in the item selection phase and agreed on by the core development group.

2.5 | CholU-QoL validation

For the validation of the CholU-QoL, we asked a total of 197 CholU patients of the Urticaria Center of Reference and Excellence (UCARE), Charité—Universitätsmedizin Berlin whether they are interested in participation in our study. During a period of 15 months, we recruited 69 patients. The UCARE at the Department of Dermatology, University Medical Center Mainz recruited 19 patients during a period of 6 months. Thus, in total, 88 CholU patients were included in the CholU-QoL validation phase. Both centres are tertiary care centres.

In this phase, a survey study was performed with all selected CholU-QoL items (the final CholU-QoL) and several anchors, that is a patient's global assessment (PGA) of disease activity (PGA-disease activity) and CholU-related QoL impairment (PGA-QoL), the Dermatology Life Quality Index (DLQI),^{17,18} the urticaria control test (UCT)¹⁹ and the CholUAS7.⁴ For test-retest reliability analysis, patients were asked to complete the survey twice with a minimal interval of 3 weeks.

2.6 | Exploratory factor analysis

To determine the domain structure of the CholU-QoL, an exploratory factor analysis was performed by use of principal component analysis with varimax rotation and Kaiser normalization.²⁰⁻²² Missing values were excluded pairwise. An eigenvalue ≥ 1 was chosen to determine factors (domains). Items were assigned to the domains for which they showed the highest factor loading. The core development group reviewed the results and made single exceptions for reasons of face validity.

2.7 | Internal consistency reliability

The internal consistency reliability of the CholU-QoL total score and its domain scores were determined by calculating the Cronbach's α coefficient. This coefficient is commonly interpreted as: $<.60$ unacceptable, $.60-.65$ undesirable, $.65-.70$ minimally acceptable, $.70-.80$ respectable, $.80-.90$ excellent, $>.90$ excessive consistency.^{20,22}

2.8 | CholU-QoL score computation

Each CholU-QoL item was scored from 0 to 4 points (0 = "not at all"/"no treatment"; 1 = "somewhat"; 2 = "moderately"; 3 = "much"; 4 = "very much"). The raw total score and the raw domain scores were calculated by adding up all respective item scores. Subsequently, all raw scores were linearly transformed to a 0-100 scale with higher scores indicating higher QoL impairment. The total score was not computed when $>20\%$ of the items (>5 items) were missing. The domain scores "symptoms," "functional life," "social interaction" and "emotions" were not computed when more than 25% of the

items were missing in the respective domain. The domain score "therapy" was not computed when $>50\%$ of the items were missing. A total of 21 items throughout all analysed 88 questionnaires were missing (percentage of missing items = 0.85%).

For the CholU-QoL total score, it was expected that patients with a higher CholU-QoL score also score higher in the PGA-QoL (correlation coefficient r of at least .5).

2.9 | Convergent validity

The CholU-QoL total and domain scores were correlated for convergent validity with the following anchors:

1. PGA-disease activity-VAS and -LS: The patients' global assessment of disease activity visual analogue scale (PGA-disease activity-VAS) assesses urticaria activity during the previous 2 weeks on a 10-cm unmarked line anchored at the 2 ends with "no complaints" (0 cm) and "maximal complaints" (10 cm).²³

The patients' global assessment of disease activity on a 4-point Likert scale (PGA-disease activity-LS) also assesses disease activity during the previous 2 weeks with the options "no complaints," "mild complaints," "moderate complaints" and "severe complaints."¹⁶

2. CholUAS7: In the daily diary, patients were asked to document the intensity of itch (Itchday: none = 0, mild = 1, moderate = 2, severe = 3), the intensity of wealing (Wealday: none = 0, mild = 1, moderate = 2, severe = 3) as well as their exposure to elicitors of symptom development, for example physical exercise, and the intensity of the elicitor they were exposed to (Intensity of elicitor day: no exposure to elicitors = 4, exposure to mild elicitor = 3, exposure to moderate elicitor = 2, exposure to strong elicitor = 1). The disease-specific disease activity score CholUAS7 was calculated as the 7-day sum of [(Wealday + Itchday) $\times$ Intensity of elicitor day].⁴ Thirty-six patients completed the daily diary. For computing the CholUAS7, the last consecutively completed 7 days were used, and the CholUAS7 scores were correlated with CholU-QoL total scores.
3. UCT: The UCT is a 4-item questionnaire with a recall period of 4 weeks to assess disease control in patients with chronic urticaria (spontaneous and inducible). Each UCT item has 5 answer options (0-4 points). Accordingly, the UCT total score ranges from 0 to 16 points. Low points indicate high disease activity and poor disease control, whereas higher values are indicative for higher levels of disease control.¹⁹
4. PGA-QoL-VAS and -LS: The patients' global assessment of quality-of-life VAS (PGA-QoL-VAS) assesses health-related QoL impairment during the previous 2 weeks on a 10-cm unmarked line anchored at the 2 ends with "no impairment of quality of life" (0 cm) and "maximal impairment of quality of life" (10 cm).²³

The patients' global assessment of quality of life on a 4-point Likert scale (PGA-QoL-LS) assesses health-related QoL impairment

with the options “no impairment,” “mild impairment,” “moderate impairment” and “severe impairment.”¹⁶

5. DLQI: The DLQI questionnaire¹⁷ measures skin health-related QoL, has a recall period of 7 days, consists of 10 questions, 6 subheadings (“symptoms and feelings,” “daily activities,” “leisure,” “work and school,” “personal relationships” and “treatment”) and has a score that ranges from 0 to 30, with 0-1 points indicating no effect at all on the patient's life, 2-5 points: small effect on patient's life, 6-10 points: moderate effect on patient's life, 11-20 points: very large effect on patient's life, and >20 points: extremely large effect on patient's life.

To assess the convergent validity of the CholU-QoL, the total and the domain scores were correlated (Spearman's correlation) with the anchors PGA-disease activity-VAS, PGA-disease activity-LS, CholUAS7, UCT score, PGA-QoL-VAS, PGA-QoL-LS, DLQI score. For the convergent validity, a high correlation ($r > .5$) and a statistically significant correlation ($P < .05$) between the CholU-QoL scores and the different anchors were anticipated. Furthermore, we expected a higher correlation of the CholU-QoL with the health-related QoL anchors (eg, DLQI) as compared to the correlation of the CholU-QoL with the anchors for disease activity and control.

2.10 | Known-groups validity

Patients with different levels of disease activity (PGA-disease activity-LS) and QoL impairment (PGA-QoL-LS) and also different levels of disease control (UCT) were compared regarding their CholU-QoL total scores.

2.11 | Test-retest reliability

Thirty-seven CholU patients, whose therapy did not change, completed all items twice in a mean interval of 12 weeks (mean $\pm$ SD: 12.5 ± 9.6 weeks; median 10; range 3-29). To determine the test-retest reliability of the CholU-QoL, we compared the CholU-QoL scores of (i) all 37 patients whose therapy did not change and (ii) 23 patients whose therapy did not change and whose PGA-disease activity-LS rating did not change from the first to the second assessment. The mean values of the 2 assessments were compared, and the intraclass correlation coefficient (ICC) was calculated. An ICC of .5-.7 represents moderate to good reproducibility, an ICC $> .7$ excellent reproducibility.^{19,24,25} As model for ICC computation, 2-way mixed effects model and absolute agreement were chosen.

For health-related QoL instruments, at least moderate test-retest reliability is requested. Higher ICC values were expected in the subgroup of 23 patients with stable disease.

2.12 | Multiple linear regression analysis

Age (in years), gender and duration of disease (in years) were included in the multiple regression analysis (as independent variables)

to detect drivers of the CholU-QoL total score (set as dependent variable).

2.13 | Development of an US American-Canadian English version of the CholU-QoL

To develop a linguistically validated US American-Canadian English version of the CholU-QoL,^{26,27} 2 independent forward translations of the German CholU-QoL version to English were conducted by native English speakers bilingual in German. The 2 translations were reconciled by 2 medical experts, Thomas Casale (US American English) and Gordon Sussmann (Canadian English), which resulted in one version. This US American-Canadian Version was subsequently back-translated to German by 2 independent German native speaker bilingual in English. The backward translations were then reviewed against the original German version and inconsistencies discussed and resolved together with the German and US/Canadian experts. Eleven American/Canadian patients between 18 and 69 years old had filled out the translated CholU-QoL. Patients were asked for confusion or difficulties in understanding the instructions or questions. Nine patients had no confusions or comments for improvement of the score. Two patients had difficulties in discriminating weals and skin redness. Accordingly, explanatory sentences in the introduction were included. The final version of the CholU-QoL was then again reviewed by the core development group and the healthcare professionals of the target language.

2.14 | Statistical analyses

Statistical analyses were performed using Microsoft Excel Version 2013 and IBM SPSS (Version 19; IBM corporation, Armonk, NY, USA). The statistical methods applied are described in the respective section of the Materials and methods. $P < .05$ was considered to indicate statistical significance. Missing values were excluded pairwise in all statistical analyses.

3 | RESULTS

3.1 | CholU-QoL item generation and selection

The item generation phase resulted in 96 items possibly relevant for CholU patients. In the subsequent item selection phase, a total of 50 CholU patients took part. All of them (100%) stated no problems with understanding the items, 30 patients (60%) found it comprehensive and 20 patients (40%) gave comments about missing or improvable items that were reviewed by the core development group and frequent comments, for example regarding assessment duration, were respected in the item selection phase.

The impact analysis (see Table 1) revealed 37 items with an impact score >2.5 points. During the expert review for face validity, 10 of these 37 items (p6, p41, p42, p44, p48, p55, p56, p57, p61, p91) were excluded due to redundancy. In addition, items p3, p24, p40 and p81 were eliminated because of perceived impreciseness. On the other hand, items p64 “burden due to treatment?” p66

TABLE 1 Impact analysis

Item no.	Item	Frequency	Importance (mean)	Impact
p1	Weals	0.979	4.09	4.00
p2	Skin redness	0.915	3.94	3.61
p3	Facial swelling	0.696	3.67	2.55
p4	Swelling of the throat and pharynx	0.489	3.36	1.64
p5	Itch	0.979	4.22	4.13
p6	Skin tingling	0.771	3.27	2.52
p7	Skin burning	0.553	2.96	1.64
p8	Skin pain	0.326	2.67	0.87
p9	Skin stinging	0.426	2.73	1.16
p10	Distension of the skin	0.583	2.79	1.63
p11	Sensation of heat	0.875	3.64	3.19
p12	Sweat	0.787	3.55	2.79
p13	Dizziness	0.565	3.07	1.73
p14	Tremors	0.457	2.87	1.31
p15	Weakness	0.638	3.34	2.13
p16	Circulatory complaints	0.636	3.21	2.04
p17	Fatigue	0.745	3.64	2.71
p18	Lethargy	0.681	3.26	2.22
p19	Weariness	0.652	3.09	2.01
p20	Exhaustion	0.711	3.47	2.47
p21	Stomach pain	0.467	2.7	1.26
p22	Joint pain	0.348	2.75	0.96
p23	Headache	0.522	3.11	1.62
p24	General malaise	0.804	3.64	2.93
p25	School/university/work	0.884	4.15	3.67
p26	Leisure time	0.957	4.13	3.95
p27	Daily activities	0.956	4.02	3.84
p28	Sport/physical activities	0.953	4.17	3.97
p29	Personal hygiene	0.714	3.12	2.23
p30	Social relationships	0.720	3.43	2.47
p31	Activities with other people	0.780	3.38	2.64
p32	Partnership	0.653	3.21	2.10
p33	Love life	0.646	3.3	2.13
p34	Sex life	0.667	3.36	2.24
p35	Sleep	0.653	3.27	2.14
p36	Eating and drinking	0.520	3.08	1.60
p37	Clothing choices	0.837	3.35	2.80
p38	Difficulties falling asleep	0.667	3.17	2.11
p39	Tired during the day	0.667	3.15	2.10
p40	Concentration difficulties	0.787	3.35	2.64
p41	Limited in performance	0.917	3.82	3.50
p42	Accomplished less	0.833	3.56	2.97
p43	Limitation in strenuous activities	0.854	3.82	3.26

(Continues)

TABLE 1 (Continued)

Item no.	Item	Frequency	Importance (mean)	Impact
p44	Avoid exhausting activities	0.830	3.7	3.07
p45	Limitation in being active	0.958	3.86	3.70
p46	Mobility	0.771	3.63	2.80
p47	Choice of cosmetics	0.604	2.91	1.76
p48	Impaired in appearance/look	0.840	3.48	2.92
p49	Appearance of urticaria	0.860	3.56	3.06
p50	Limit wish to be with other people	0.820	3.49	2.86
p51	Stay at home	0.820	3.34	2.74
p52	Do things alone	0.660	3.16	2.09
p53	Feel uncomfortable in public	0.820	3.73	3.06
p54	Avoiding to visit public places	0.694	3.38	2.35
p55	Ashamed because of urticaria	0.755	3.48	2.63
p56	Embarrassing	0.776	3.4	2.64
p57	Fear of being watched in public because of scratching	0.840	3.34	2.81
p58	Feel uncomfortable because of scratching	0.860	3.36	2.89
p59	Fear of further course of disease	0.840	3.69	3.10
p60	Uncertainty	0.800	3.53	2.82
p61	Unpredictability	0.776	3.54	2.75
p62	Fear of physical contact	0.540	2.87	1.55
p63	Fear of asphyxiation	0.560	3.08	1.72
p64	Burden due to treatment	0.694	3.53	2.45
p65	Impaired because of therapy	0.653	3.2	2.09
p66	Worried about drug side-effects	0.673	3.15	2.12
p67	Drug side-effects	0.673	3.08	2.07
p68	Impaired because of drug side-effects	0.583	2.98	1.74
p69	Frustrated	0.776	3.08	2.39
p70	Bad	0.604	2.94	1.78
p71	In a bad mood	0.673	2.86	1.92
p72	Downcast	0.755	2.92	2.20
p73	Depressed	0.792	3.06	2.42
p74	Depressive	0.571	2.86	1.63
p75	Humiliated	0.449	2.43	1.09
p76	Dispirited	0.653	2.84	1.85
p77	Sad	0.633	3.18	2.01
p78	Lonely	0.367	2.71	0.99

(Continues)

TABLE 1 (Continued)

Item no.	Item	Frequency	Importance (mean)	Impact
p79	Helpless	0.694	3.02	2.10
p80	Unconscious	0.449	2.38	1.07
p81	Stressed/burdened	0.833	3.38	2.82
p82	Ashamed	0.638	2.86	1.82
p83	Embarrassed	0.500	2.51	1.26
p84	Biased	0.583	2.47	1.44
p85	Annoyed (irritated)	0.833	3.14	2.62
p86	Irritable	0.750	3.2	2.40
p87	Upset	0.681	2.88	1.96
p88	Exhausted	0.729	3.14	2.29
p89	Tired	0.667	3.06	2.04
p90	Powerless	0.563	2.94	1.66
p91	Less powerful	0.792	3.21	2.54
p92	Inhibited	0.646	2.71	1.75
p93	Doubtful	0.583	2.69	1.57
p94	Nervous	0.646	2.82	1.82
p95	Scared	0.542	2.61	1.41
p96	Useless	0.375	2.24	0.84

High impact scores (>2.5) are printed in boldface.

“worried about drug side-effects,” p67 “drug side-effects,” p69 “frustrated” and p73 “depressed” slightly failed the >2.5 point cut-off, but were regarded as important by the core development group and included in the final CholU-QoL item set. The wording of item p12 was slightly modified to make it more precise. Finally, 28 items were selected for the final CholU-QoL questionnaire.

3.2 | CholU-QoL validation and first results

In the validation study, a total of 88 CholU patients were included (patient characteristics see Table 2). The explorative factor analysis revealed a 5-domain structure of the CholU-QoL (Table 3) that explained 76.3% of its variance. According to the content of the assigned items, the 5 domains were termed “symptoms,” “functional life,” “social interaction,” “therapy” and “emotions.” Items were assorted to the domain with the highest factor loading. All but one item (sweat) could be accordingly assigned to one of the domains. The item “sweat” was sorted to the domain “functional life” by the core development group for reasons of face validity, although its factor loading was highest for the domain “emotions.” In the last step, the items were rearranged according to the CholU-QoL domain structure. The German and US American-Canadian English versions of the CholU-QoL are available as Supporting Information (see Appendices S1 and S2).

3.3 | Internal consistency reliability

Each CholU-QoL domain was tested for its internal consistency by computing the Cronbach's α coefficient (Table 4). The Cronbach's α

TABLE 2 Patient sample characteristics of CholU-QoL validation study

	n	%
Gender (n = 88)		
Female	59	67
Male	29	33
Age (n = 88)		
18-30 yrs	37	42
31-50 yrs	34	38.6
51-70 yrs	15	17
>70 yrs	2	2.3
Duration of cholinergic urticaria (n = 86)		
≤5 yrs	41	47.7
6-15 yrs	32	37.2
16-25 yrs	5	5.8
26-35 yrs	5	5.8
>35 yrs	3	3.5

coefficient was >.9 for the domains “functional life,” “social interaction” and “emotions,” indicating excessive consistency and >.8 for the domains “symptoms” and “therapy,” indicating excellent internal consistency. In addition, the Cronbach's α coefficient for the CholU-QoL total score was found to be .97, indicating that it is appropriate to compute a total score in addition to the 5 domain scores.

3.4 | CholU-QoL results

The results of the CholU-QoL total and the domain scores of the validation study are shown in Figure 1. The distribution of the total and the domain scores was overall broad. Three patients (3.4%) scored the lowest possible total score of 0. No patient scored the highest possible total score of 100 points. The highest total score that was reached was 91 points.

3.5 | Convergent validity

The convergent validity was tested by correlating the CholU-QoL total and domain scores with the results of the anchor instruments (see Table 5). All correlations were significant and in the expected directions. The correlation coefficient was high ($r > .8$) for the correlations of the total scores, except for the correlation of the CholU-QoL scores with the CholUAS7 ($r > .45$). The highest correlation was seen between the CholU-QoL total score and the DLQI score ($r = .88$).

3.6 | Known-groups validity

Patients with different levels of disease activity (PGA-disease activity-LS) and QoL impairment (PGA-QoL-LS) had significant differences in CholU-QoL total scores (see Table 6). As expected, the CholU-QoL total score increased with increasing levels of disease activity and health-related QoL impairment. The interquartile range of the

TABLE 3 Factor analysis

Items	Factor 1 (symptoms)	Factor 2 (functional life)	Factor 3 (social interaction)	Factor 4 (therapy)	Factor 5 (emotions)
Weals	0.582	0.380	0.339	−0.057	0.197
Skin redness	0.687	0.245	0.391	0.037	0.258
Itch	0.615	0.423	0.219	−0.094	0.180
Sensation of heat	0.544	0.309	0.255	−0.008	0.476
Fatigue	0.725	0.150	0.075	0.345	0.250
School/university/work	0.482	0.609	0.277	0.238	0.223
Leisure time	0.358	0.732	0.235	0.048	0.309
Daily activities	0.477	0.673	0.076	0.130	0.305
Sport/physical activities	0.227	0.742	0.218	−0.002	0.419
Activities with other people	0.274	0.723	0.371	0.126	0.166
Clothing choices	0.495	0.511	0.205	0.221	0.099
Limitation in strenuous activities	0.197	0.722	0.205	0.152	0.404
Limitation in being active	0.259	0.701	0.226	0.072	0.499
Sweat	0.123	0.532	0.286	0.132	0.611
Mobility	0.308	0.586	0.038	0.213	0.456
Stay at home	0.126	0.653	0.500	0.217	0.141
Appearance of urticaria	0.326	0.288	0.744	0.025	0.273
Limit wish to be with other people	0.223	0.567	0.609	0.222	0.170
Feel uncomfortable in public	0.202	0.569	0.590	0.078	0.389
Feel uncomfortable because of scratching	0.375	0.270	0.652	0.073	0.305
Burden due to treatment	0.015	0.283	−0.169	0.726	0.375
Worried about drug side-effects	0.028	0.031	0.151	0.827	0.249
Drug side-effects	0.125	0.092	0.145	0.861	−0.062
Annoyed (irritated)	0.347	0.290	0.185	0.149	0.723
Frustrated	0.192	0.359	0.236	0.122	0.765
Depressed	0.303	0.391	0.113	0.214	0.710
Fear of further course of disease	0.239	0.231	0.470	0.198	0.625
Uncertainty	0.177	0.150	0.415	0.343	0.565

Items with a factor loading >0.5 are printed in boldface.

CholU-QoL total scores of the different levels of disease activity and the health-related QoL impairment did not overlap, except for a small overlap of .5 points in the disease activity categories “mild” and “moderate.”

Furthermore, patients with uncontrolled symptoms (UCT < 11) scored higher in the CholU-QoL as compared to patients with controlled disease (UCT > 12). Again, the interquartile ranges did not overlap.

3.7 | Test-Retest reliability

When we analysed the scores of 37 patients, who completed the CholU-QoL twice, for test-retest reliability, CholU-QoL total and domain scores were not significantly different between the 2 time-points (see Table 7). The ICC was .85 for the total score and

between .76 and .86 for the domains “symptoms,” “functional life” and “social interaction” indicating excellent reproducibility (>.75). The ICC was lower for the domains “therapy” and “emotions” (.66 and .67), but still indicated moderate reproducibility. The ICC of the 23 patients with both criterions for disease stability fulfilled was .94 for the CholU-QoL total score and >.80 for all domains, except the domain “therapy” (.67) (see Table 8).

3.8 | Influence factors of the CholU-QoL total score

The multiple linear regression analysis did not reveal a significant influence of age, gender or duration of disease on the CholU-QoL total score (see Table 9).

TABLE 4 Domain structure and internal consistency of the CholU-QoL

Domain	Item	Cronbach's α
Symptoms (n = 85)	Wheals	.865
	Skin redness	
	Itch	
	Sensation of heat	
	Fatigue	
Functional life (n = 82)	School/university/work	.960
	Leisure time	
	Daily activities	
	Sport/physical activities	
	Activities with other people	
	Clothing choices	
	Limitation in strenuous activities	
	Limitation in being active	
	Sweat	
	Mobility	
	Stay at home	
Social interaction (n = 87)	Appearance of urticaria	.917
	Limit wish to be with other people	
	Feel uncomfortable in public	
	Feel uncomfortable because of scratching	
Therapy (n = 87)	Burden due to treatment	.813
	Worried about drug side-effects	
	Drug side-effects	
Emotions (n = 87)	Annoyed (irritated)	.918
	Frustrated	
	Depressed	
	Fear of further course of disease uncertainty	
Total instrument (n = 78)		.971

4 | DISCUSSION

Here, we report the development and validation of the first CholU-specific QoL measure. The final CholU-QoL has 28-items, a 5 domain structure and a valid total score. CholU-QoL total scores and domain scores in the validation study were broad, demonstrating that CholU patients exhibit a considerable variation in QoL impairment. This makes sense as the patient population included in the study consisted of patients with different levels of disease activity, similar to the real-life daily care situation.

When looking at single CholU-QoL domains, we found that the domain "emotions" was most affected. However, the differences between the mean scores of the domains were rather small (between 39 and 44 points), except for the domain "therapy" with a mean score of 20 points. The small differences indicate an overall comparable impact of CholU on the different aspects of disease-related QoL represented by the 5 domains. The exception of the domain "therapy" may be explained by the way of computation of this domain score. "No treatment" was scored in the same way as

the option "not at all" with 0 points. This computing was suggested by the core development group, as it was supposed that a patient who had a treatment that provokes additional side-effects has a stronger QoL impairment compared to a patient with no treatment. When computing the domain score "therapy" only for the 60 patients who had treatment, the resulting mean domain score was 30.0 (see Figure 1), which is within the range of the results of the remaining subdomains.

The levels of convergent validity of the CholU-QoL total and domain scores with all anchor scores exceeded our expectations, except for the domain "therapy," most likely because not all patients had treatment and not all anchor instruments included questions on therapy. As anticipated, we determined that the correlation of the CholU-QoL with the QoL anchor, DLQI, was higher than the correlation with the anchors of disease activity (eg, CholUAS7). The reason is that the DLQI is conceptually closer to the CholU-QoL than the disease activity measures, and it is well known that disease activity usually only moderately correlates with QoL impairment.²⁸ The correlation of the UCT score and the CholU-QoL total score was also high and statistically significant, which shows a significant relation between the different levels of disease control and the impairment of QoL.

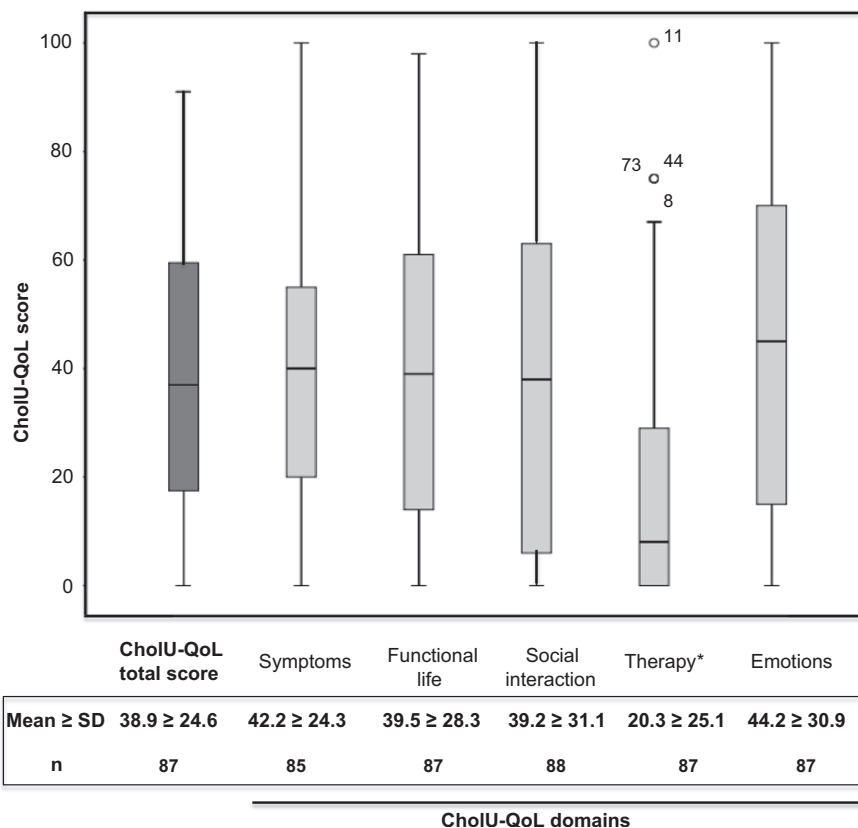
In the known-groups validity assessment of the CholU-QoL, the total score was different in patients with different levels of disease activity, globally rated QoL impairment and different levels of disease control. The very good results of the known-groups validity indicate the high discriminative ability of the CholU-QoL. Interestingly, this analysis clearly depicted the broad variation in QoL impairment in CholU patients, where many patients (58%) had no or mild interference in their life, but also 15% of the CholU patients had maximum QoL impairment (see Table 6). Furthermore, the UCT analysis showed that in 67%, the disease could not be controlled by the current therapy of the patients.

In the test-retest reliability analysis of the CholU-QoL, the ICC was excellent in stable patients, except for moderate to good reproducibility for the domains "therapy" and "emotions." The lower ICC for these domains may be due to the fact that the items of these domains assess the personal feelings of patients or their attitude towards the therapy (eg, anxiety, capacity to suffer), which can vary substantially. Another factor could be that the interval between the first and the second assessments was quite long in some patients, up to 29 weeks, and varied considerably.

Interestingly, the multiple linear regression analysis identified no significant influence factor on the CholU-QoL total score. This result is in contrast to similar QoL instruments, in which an influence of duration of disease²⁹ or of gender²² was seen. These results showed that in CholU women and men, young and old suffer to same extent, and it does not matter how long the CholU persists.

The CholU-QoL is a 28-item questionnaire, which is easy and fast to complete for patients. In our experience, it takes patients <5 minutes to complete the CholU-QoL and it only takes another minute to calculate the total and domains scores. Twenty-eight is a fair number of items for a QoL instrument and comparable with

FIGURE 1 Total Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-QoL) and domain scores. The domain “emotions” ($n = 87$) had the highest mean score of 44.2 ± 30.9 (mean score $\pm$ SD). The domain “symptoms” ($n = 85$) scored 42.2 ± 24.3 , “functional life” ($n = 87$) scored 39.5 ± 28.3 , “social interaction” ($n = 88$) scored 39.2 ± 31.1 and “therapy” ($n = 87$) scored 20.3 ± 25.1 *. The total score ($n = 87$) was 38.9 ± 24.6 . *The domain “therapy” is computed with 87 patients, but only 60 of them have had a treatment because of their urticaria. The other 27 patients had no treatment and scored with 0 points, accordingly. When computing the domain therapy only with the 60 patients who have had a treatment, the mean score is 30.0 ± 25.3 (mean $\pm$ SD)



other tools such as the mastocytosis quality-of-life questionnaire (MC-QoL) with 27 items,²⁹ the German Version of ItchyQoL (Ger-ItchyQoL) with 22 items²¹ and the Chronic Urticaria Quality-of Life questionnaire (CU-Q2oL) with 23 items.⁹

The strengths of this work include that we investigated patients with a broad range of disease durations, disease activity and of different age classes, recruited independently at 2 centres, and that the CholU-QoL was correlated with many different validated QoL anchors, but also with specific disease activity (CholUAS7) and disease control (UCT) scores.

Limitations of this work include (i) that the development of the CholU-QoL did not include children with CholU and that we do not know yet how the CholU-QoL performs in older children and adolescents, (ii) that the sensitivity to change and the minimal important difference in the CholU-QoL have not been studied. The latter has to be performed in future studies to find out which score changes in the CholU-QoL overtime can be considered a meaningful change to the patient.¹¹ (iii) The sample size in our study was limited to 88 patients, as it was difficult to find more patients with confirmed diagnostic criteria of CholU, who were willing to participate in our study within a reasonable time frame. Despite this limitation computations showed good results, and most likely would not give different results in a higher number of patients. (iv) Some of the patients included in this study had concomitant diseases including other forms of chronic urticaria. We decided to include these patients, because the coexistence of other conditions, for example a combination of different forms of chronic urticaria in the same patient is a common feature of all types of

chronic urticaria including cholinergic urticaria.^{30,31} Of note, all patients in this study had confirmed diagnostic criteria of CholU and CholU, in patients with more than one type of chronic urticaria, was the dominant urticaria type.”

As of yet, a German and an US American-Canadian English version of the CholU-QoL is available. To make this tool broadly available for future multinational trials, a linguistic validation for additional languages is desirable, similar to the approach used for other patient-reported outcomes in urticaria and angioedema.^{20,32} Future studies that use the CholU-QoL should look at the influence of treatment on QoL impairment^{6,33,34} and the link of QoL impairment and psychological resources in CholU patients.³⁵

In conclusion, the CholU-QoL is the first instrument with excellent validity and reliability for the assessment of disease-specific QoL impairment in patients with CholU, which may be used as an index instrument to measure the overall CholU-related QoL impairment and as a profile instrument for distinct aspects and patterns of CholU-related QoL impairment. It may serve as a valuable tool in future clinical trials in this understudied condition and to improve and standardize the assessment and documentation in routine patient management. The CholU-QoL may particularly help to better determine and monitor the extent as well as the profile of health-related QoL impairment in CholU patients.

ACKNOWLEDGEMENTS

The development of the CholU-QoL was cofounded by the International Institute of Dermatological Allergology (I²DEAL) at Charité.

TABLE 5 Convergent validity of the CholU-QoL. Correlations were computed between the CholU-QoL scores and the Dermatology Life Quality Index (DLQI) scores, urticaria control test (UCT) scores, patient's global assessment (PGA)-disease severity-VAS, PGA-disease severity-LS, PGA-QoL-VAS, PGA-QoL-LS and CholUAS7. The results are expressed as Spearman's correlation coefficients

	CholU-QoL scores					
	Total score	Symptoms	Functional life	Social interaction	Therapy	Emotions
DLQI (n = 84-88)						
Total score	.881***	.718***	.907***	.775***	.419***	.765***
Symptoms and feelings	.793***	.735***	.783***	.745***	.267*	.690***
Daily activities	.692***	.547***	.747***	.564***	.295**	.590***
Leisure	.782***	.573***	.811***	.698***	.390***	.666***
Work and school	.620***	.557***	.582***	.536***	.396***	.562***
Personal relationships	.634***	.491***	.647***	.585***	.377***	.531***
Treatment	.370***	.314**	.401***	.296**	.250*	.318**
UCT ^a (n = 77-88)						
Total score	-.827***	-.751***	-.814***	-.766***	-.343**	-.752***
Symptoms	-.757***	-.760***	-.752***	-.681***	-.202	-.686***
QoL	-.844***	-.763***	-.833***	-.744***	-.370***	-.787***
Treatment	-.661***	-.508***	-.651***	-.598***	-.407***	-.627***
Disease control	-.723***	-.740***	-.681***	-.723***	-.135	-.661***
PGA (n = 84-88)						
PGA-disease severity-VAS	.809***	.850***	.772***	.739***	.219*	.727***
PGA-disease severity-LS	.770***	.839***	.714***	.708***	.220*	.676***
PGA-QoL-VAS	.861***	.824***	.848***	.740***	.357**	.796***
PGA-QoL-LS	.840***	.785***	.824***	.743***	.370***	.758***
Diary (n = 31-32)						
CholUAS7	.497**	.584**	.484**	.362*	.062	.407*

^aCorrelations with the UCT are negative, because, in contrast to CholU-QoL, lower scores in this instrument represent a stronger QoL impairment.

* $P < .05$; ** $P < .01$; *** $P < .001$.

TABLE 6 Known-groups validity of the CholU-QoL. The results are expressed as CholU-QoL total score in relation to the patients' self-rated disease activity and QoL impairment and the urticaria control test (UCT) score

	n	CholU-QoL total score mean $\pm$ SD (median)	1st quartile	3rd quartile
PGA ^a disease activity				
None ^b	4	0.75 $\pm$ 1.50 (0.0)	0.0	2.3
Mild	41	25.02 $\pm$ 16.93 (21.0)	12.0	36.5
Moderate	28	47.75 $\pm$ 15.48 (51.5)	36.0	60.8
Severe	14	72.79 $\pm$ 12.66 (72.0)	63.0	86.0
PGA ^a QoL impairment ^c				
None	18	10.44 $\pm$ 12.50 (5.5)	3.0	13.8
Mild	32	31.91 $\pm$ 15.45 (29.5)	19.5	39.5
Moderate	23	52.09 $\pm$ 10.97 (53.0)	42.0	63.0
Severe	13	74.69 $\pm$ 11.21 (72.0)	68.5	86.0
UCT score ^d				
>11 points	26	16.46 $\pm$ 14.20 (14.5)	3.0	23.8
<12 points	53	51.02 $\pm$ 20.78 (54.0)	35.0	65.5

^aPatients global assessment (PGA) with regard to the previous 2 wks.

^bOne patient who also had chosen "none" was excluded because the CholU-QoL total score could not be calculated.

^cThere were 2 missing data for QoL impairment.

^dIn contrast to CholU-QoL, lower scores in this instrument represent a stronger QoL impairment.

TABLE 7 Test-retest reliability of the CholU-QoL. A subsample of 37 patients completed the CholU-QoL twice in an interval of at least 3 weeks. The results are expressed as mean CholU-QoL scores as well as intraclass correlation coefficient (ICC)

CholU-QoL	Mean score $\pm$ SD (1st assessment) n = 35-37	Mean score $\pm$ SD (2nd assessment) n = 36-37	ICC n = 34-37
Total score	40.3 $\pm$ 27.9	36.5 $\pm$ 26.4	.846
Symptoms	45.4 $\pm$ 26.7	39.6 $\pm$ 25.8	.863
Functional life	41.0 $\pm$ 32.7	40.3 $\pm$ 32.1	.853
Social interaction	39.3 $\pm$ 33.4	34.9 $\pm$ 31.5	.764
Therapy	21.7 $\pm$ 27.9	20.5 $\pm$ 24.8	.660
Emotions	43.4 $\pm$ 31.4	37.4 $\pm$ 30.1	.666

TABLE 8 Test-retest reliability of the CholU-QoL in 23 patients whose therapy did not change and both corresponding patient's global ratings of disease severity (patient's global assessment-disease severity-LS) showed identical results. The results are expressed as mean CholU-QoL scores as well as intraclass correlation coefficient (ICC)

CholU-QoL	Mean score $\pm$ SD (1st assessment) n = 22-23	Mean score $\pm$ SD (2nd assessment) n = 22-23	ICC n = 21-23
Total score	41.5 $\pm$ 29.1	37.5 $\pm$ 28.4	.940
Symptoms	45.9 $\pm$ 27.6	42.7 $\pm$ 26.1	.961
Functional life	42.5 $\pm$ 33.6	40.7 $\pm$ 34.6	.975
Social interaction	38.7 $\pm$ 33.5	34.7 $\pm$ 30.2	.868
Therapy	24.3 $\pm$ 30.0	23.5 $\pm$ 27.7	.670
Emotions	44.1 $\pm$ 33.7	37.8 $\pm$ 31.8	.800

TABLE 9 Influence factors of the CholU-QoL. Multiple linear regression analysis identified that there is no significant influence factor of the CholU-QoL total score

	n	Unstandardized coefficient B	Standard error	P-value
Gender	88	−6.899	5.740	.233
Age (in years)	88	−.115	0.198	.562
Disease duration (in years)	86	.270	0.287	.350

This project was supported by the GA²LEN UCARE programme (<http://www.ga2len.net/ucare.html>). We thank Jodie Urcioli and Elke Rooks for help in the translation process and all the patients who participated in the study.

CONFLICTS OF INTERESTS

Jessica Ruft, Aida Asady, Petra Staubach and Torsten Zuberbier have no conflicts of interests to declare. Thomas Casale has been an investigator and consultant for Novartis and Genentech with all fees to his university employer. Gordon Sussman is a consultant, speaker and/or

Principal Investigator for Novartis, GSK, AstraZeneca, Aimmune, DBV Technologies, GreenCross, BioCryst, Kendrion, CSL Behring, Genentech, Stallergenes, Dyax/Shire, Merck, Pfizer, Sanofi Pasteur, Aralez and Pediapharm. Marcus Maurer has acted received funds for research from Moxie GmbH. Karsten Weller received honoraria for educational lectures from MOXIE GmbH. Sabine Altrichter has acted received payment for speaking from Moxie GmbH.

AUTHOR CONTRIBUTIONS

J. Ruft: Clinical data acquisition, patient recruitment, member of the core development group, statistical analysis, manuscript writing, study coordination. A. Asady: Patient recruitment. P. Staubach: Patient recruitment at University Medical Center Mainz. T. Casale: Linguistic validation process. G. Sussman: Linguistic validation process. T. Zuberbier: Linguistic validation process. M. Maurer: Lead of study center, proof-reading. K. Weller: Study coordination, proof-reading, statistical review, member of the core development group. S. Altrichter: Study leader, study coordination, member of the core development group, manuscript writing.

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SUPPORTING INFORMATION

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How to cite this article: Ruft J, Asady A, Staubach P, et al. Development and validation of the Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-QoL). *Clin Exp Allergy*. 2018;48:433–444. <https://doi.org/10.1111/cea.13102>

CholU-QoL

Fragebogen zur Lebensqualität von Patienten mit cholinergischer Urtikaria

Anleitung: Liebe Patientinnen und Patienten, Sie leiden unter einer cholinergischen Urtikaria. Hierbei kommt es neben Juckreiz zu Quaddeln und/oder Rötungen der Haut durch körperliche Anstrengung, Schwitzen oder eine andere Art der Erwärmung, wie zum Beispiel durch heiße Bäder oder Sauna. Quaddeln sind scharf begrenzte, leicht erhabene und damit tastbare, gerötete Hautveränderungen. Hautrötungen sind ebenfalls scharf begrenzt, aber nicht erhaben und damit nicht tastbar. In diesem Fragebogen finden Sie Fragen zu Ihrer Lebensqualität. Bitte lesen Sie sich die Fragen durch und wählen Sie aus den gegebenen fünf Antwortmöglichkeiten diejenige aus, die für Sie am besten zutrifft. Die Fragen beziehen sich auf die letzten 14 Tage. Bitte denken Sie daran alle Fragen zu beantworten und pro Frage nur ein Kästchen anzukreuzen.

Wie sehr haben Sie in den letzten 14 Tagen unter den folgenden Beschwerden Ihrer Nesselsucht (Urtikaria) gelitten?	gar nicht	wenig	mittel-mäßig	stark	sehr stark
1. Quaddeln					
2. Hautrötungen					
3. Juckreiz					
4. Hitzegefühl					
5. Müdigkeit					

Wie sehr waren Sie in den letzten 14 Tagen in den folgenden Bereichen des täglichen Lebens durch Ihre Nesselsucht (Urtikaria) beeinträchtigt?	gar nicht	wenig	mittel-mäßig	stark	sehr stark
6. Schule / Studium / Beruf					
7. Freizeitgestaltung					
8. Tägliche Aktivitäten (z.B. Haushalt/ Einkaufen/ Gartenarbeit)					
9. Körperliche Aktivitäten / Sport					
10. Aktivitäten mit anderen Menschen					
11. Wahl der Kleidung					
12. Waren sie wegen Ihrer Nesselsucht beeinträchtigt anstrengende Tätigkeiten zu verrichten?					
13. Hat es Ihnen Ihre Nesselsucht erschwert aktiv zu sein?					
14. Haben Sie wegen Ihrer Nesselsucht Situationen oder Tätigkeiten gemieden, in denen Sie ins Schwitzen kommen?					
15. Waren Sie wegen Ihrer Nesselsucht in Ihrer Mobilität eingeschränkt?					
16. Haben Sie wegen Ihrer Nesselsucht dazu geneigt häufiger zu Hause zu bleiben?					

Mit den folgenden Fragen möchten wir näher auf Schwierigkeiten und Probleme eingehen, die mit Ihrer Nesselsucht (Urtikaria) in den letzten 14 Tagen verbunden waren:	gar nicht	wenig	mittel-mäßig	stark	sehr stark
17. Haben Sie unter der Sichtbarkeit Ihrer Nesselsucht gelitten?					
18. Hat die Nesselsucht Ihren Wunsch eingeschränkt mit anderen Menschen zusammen zu sein?					
19. Haben Sie sich wegen Ihrer Nesselsucht in der Öffentlichkeit unwohl gefühlt?					
20. War es Ihnen unangenehm, wenn andere Menschen Ihre Nesselsucht oder damit verbundenes Kratzen bemerkt haben?					

Mit den folgenden Fragen möchten wir näher auf Ihre Therapie der Nesselsucht (Urtikaria) in den letzten 14 Tagen eingehen:	gar nicht	wenig	mittel-mäßig	stark	sehr stark	keine Therapie
21. Stellte die Behandlung Ihrer Nesselsucht für Sie eine Belastung dar?						
22. Hatten Sie Sorge vor möglichen Nebenwirkungen Ihrer Nesselsuchtbehandlung?						
23. Haben Sie unter Nebenwirkungen Ihrer Nesselsuchtbehandlung gelitten?						

Fühlten Sie sich in den letzten 14 Tagen aufgrund Ihrer Nesselsucht (Urtikaria) ...?	gar nicht	wenig	mittel-mäßig	stark	sehr stark
24. genervt					
25. frustriert					
26. deprimiert					
27. Haben Sie sich Sorgen gemacht, Ihre Nesselsucht könnte sich verschlimmern?					
28. Haben Sie unter Ungewissheit gelitten, wann Ihre Nesselsuchtbeschwerden auftreten?					

Name: _____

Datum: ____ . ____ . ____

Geburtsdatum: ____ . ____ . ____

CholU-QoL

Questionnaire on quality of life of patients with cholinergic urticaria

Instructions: Dear Patient, you suffer from cholinergic urticaria. In addition to itching, it can lead to wheals and/or redness of the skin through physical activity, sweating or other methods of warming such as through hot baths or the sauna. Wheals are clearly delineated, slightly raised, and therefore palpable, red changes in the skin. Redness of the skin is also clearly delineated, but not raised, and, therefore, not palpable.

This questionnaire contains questions about your quality of life. Please read through the questions and choose the response from the five options that best applies to you. The questions pertain to the last 14 days. Please be sure to answer all of the questions and only mark one box per question.

How much have you suffered from the following symptoms of your urticaria (hives) in the last 14 days?	not at all	some-what	moder-ately	much	very much
1. Wheals					
2. Skin Redness					
3. Itch					
4. Sensation of heat					
5. Fatigue					

How much have your urticaria (hives) affected the following areas of daily life in the last 14 days?	not at all	some-what	moder-ately	much	very much
6. School / University / Work					
7. Leisure time					
8. Daily activities (shopping, housework, yard work etc.)					
9. Physical activities / Sport					
10. Activities with other people					
11. Clothing choices					
12. Was your ability to perform strenuous activities limited because of your urticaria?					
13. Did your urticaria make it more difficult to be active?					
14. Did you avoid situations or activities that could cause you to sweat because of your urticaria?					
15. Was your mobility limited because of your urticaria?					
16. Were you more likely to stay at home because of your urticaria?					

We would like to further study difficulties and problems that may be associated with your urticaria (hives) using the following questions. Please answer according to your experiences from the last 14 days .	not at all	some-what	moder-ately	much	very much
17. Did you suffer because of the appearance of your urticaria?					
18. Did your urticaria limit your wish to be with other people?					
19. Did you feel uncomfortable in public because of your urticaria?					
20. Did you feel uncomfortable when other people noticed your urticaria or scratching?					

With the following questions, we would like to learn more about your urticaria (hives) treatment in the last 14 days .	not at all	some-what	moder-ately	much	very much	no treatment
21. Was your urticaria treatment a burden for you?						
22. Were you worried about possible side effects of your urticaria treatment?						
23. Have you suffered from side effects from your urticaria treatment?						

How much in the last 14 days has your urticaria (hives) made you feel...?	not at all	some-what	moder-ately	much	very much
24. irritated					
25. frustrated					
26. depressed					
27. Have you worried that your urticaria could get worse?					
28. Have you suffered from uncertainty about when your urticaria symptoms could occur?					

name: _____

date: ____ . ____ . ____

birth date: ____ . ____ . ____