

Clinical Measures of Chronic Urticaria



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KEYWORDS

- Urticaria • Angioedema • Patient reported outcome • Disease activity
- Disease control • Quality of life

KEY POINTS

- Because of the fluctuating nature of chronic urticaria symptoms, physicians almost never see a representative picture of patients' disease and objective and specific biomarkers are not yet established. Accordingly, patient reported outcome instruments and other clinical measures are required to determine the patient's disease status.
- There are various validated and reliable clinical measures to assess patients with chronic urticaria, that is, recurrent wheals that itch, angioedema, or both.
- Disease activity can be determined by the Urticaria Activity Score, the Angioedema Activity Score, the Cholinergic Urticaria Activity Score, and, for all chronic inducible urticarias, the measurement of critical trigger thresholds.
- Disease control is determined by the Urticaria Control Test, and the impairment of health-related quality of life can be assessed by use of the Chronic Urticaria Quality of Life Questionnaire and the Angioedema Quality of Life Questionnaire.
- These clinical measures may support treatment decisions and improve the detection and documentation of treatment responses. In addition, these measures facilitate, improve, and standardize medical record keeping and, at the same time, provide new insights into patients' disease burden.

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INTRODUCTION

Chronic urticaria is a common skin disorder¹ with a high relevance in dermatologic and allergological patient care.^{2,3} It is defined by the occurrence of transient itchy wheals (hives), angioedema, or both for more than 6 weeks.⁴

Chronic urticaria is divided into chronic spontaneous urticaria (CSU) and chronic inducible urticarias (CIndUs) (Table 1).⁴ In CSU, wheals and/or angioedema occur suddenly and unpredictably without a specific trigger. The intake of nonsteroidal anti-inflammatory drugs or specific foods, stress, and physical triggers, such as heat, can prompt exacerbations in some patients; but these triggers are not specific, that is, their presence does not reproducibly lead to wheals or angioedema and wheals and angioedema also occur without these triggers. In contrast, CIndUs are characterized by specific triggers, which are required for urticaria signs and symptoms to occur and which reproducibly induce them. The development of wheals and angioedema in patients with CindU is typically but not always limited to the areas of exposure, for example, to areas of cold contact in cold urticaria. Both CSU and CIndUs frequently cause a major impairment of patients' health-related quality of life (HR-QoL).^{5–8}

As of yet, there are no established, objective, reliable, and specific biomarkers to measure the disease activity and disease control in patients with CSU and CIndU. In addition, there are no biomarkers available to assess changes of these disorders over time, for example, before and after treatment adjustment. Accordingly, clinical measures are currently the only way to assess these features as well as to assess the disease burden.

This review gives an overview of the currently available clinical measures for chronic urticaria. In addition, the authors provide information on how to best use these measures in clinical practice and the evaluation and interpretation of their results.

CLINICAL MEASURES OF CHRONIC SPONTANEOUS URTICARIA AND CHRONIC INDUCIBLE URTICARIAS

It is not trivial to determine the disease status in patients with chronic urticaria. CSU is a strongly fluctuating disorder. Many patients have daily or almost-daily symptoms;

Table 1 Classification of chronic urticaria	
CSU	CIndU
Spontaneous appearance of wheals, angioedema, or both ≥6 wk due to known or unknown causes	Symptomatic dermographism (also known as urticaria factitia) Cold urticaria (also known as cold contact urticaria) Delayed pressure urticaria (also known as pressure urticaria) Solar urticaria Heat urticaria (also known as heat contact urticaria) Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

Adapted from Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69(7):871; with permission.

but the timing of their occurrence, their severity, and duration can change considerably from day to day. In addition, symptom episodes occur particularly often during the evening, nighttime, and early morning.⁹ Accordingly, many patients do not have visible wheals or angioedema at the time of appointments with their doctors or they show up with signs and symptoms, but these are not representative for what they usually have.¹⁰ In addition, itch is not objectively assessable,¹⁰ although it is a key symptom and major driver of patients' disease burden.¹¹

In CIndUs, there is an additional factor that makes it difficult to assess the disease status: patients with CindU usually avoid the triggers of their urticaria as best as they can. This avoidance may lead to little or mild urticaria symptoms, and patients, therefore, may falsely be categorized as suffering from only mild disease, although their disease burden remains high and their CIndU is only poorly under control.

The best way to address these problems is to implement standardized, valid, and reliable clinical measures, that is, patient-reported outcome tools (PROs) and critical trigger threshold (CTT) measurements, to determine patients' disease activity, disease control, and HR-QoL impairment in routine care. In addition, the availability and use of these measures are important to improve and standardize outcome assessment in clinical studies.

PROs are questionnaires that obtain all relevant information directly from the affected patients.¹² They are typically designed to gather information on one specific topic or for one specific purpose. PROs usually result in total scores and/or several subscores that subsequently need to be interpreted by the administering health care professional.

CTTs are assessed by standardized, provocation tests that expose patients with CIndU to the specific trigger of their urticaria in graded intensity.¹³ Subsequently, patients are monitored for the occurrence of urticaria signs and symptoms. The lowest trigger intensity that still induces symptoms is the individual CTT and indicates patients' disease activity.

This article focuses on the available and specific PRO measure to determine disease activity, disease control, and HR-QoL impairment in CSU and CIndUs (Tables 2 and 3). In addition, it provides a short overview of ways to determine CTTs.

CLINICAL MEASURES OF DISEASE ACTIVITY IN CHRONIC SPONTANEOUS URTICARIA
Urticaria Activity Score

The Urticaria Activity Score (UAS) is the broadly accepted gold standard to assess disease activity in CSU and is recommended by the current guidelines.⁴ It has been used

Table 2 Relevant patient-reported outcome measures in chronic spontaneous urticaria and areas of use			
	CSU		
	Patients with Wheals (Hives)	Patients with Wheals (Hives) and Angioedema	Patients with Angioedema
Disease activity	UAS	UAS ^a and AAS ^b	AAS
Disease control	UCT	UCT	UCT
HR-QoL	CU-Q2oL	CU-Q2oL and AE-QoL	AE-QoL

Abbreviations: AAS, Angioedema Activity Score; AE-QoL, Angioedema Quality of Life Questionnaire; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; UAS, Urticaria Activity Score; UCT, Urticaria Control Test.

^a The Urticaria Activity Score does not assess angioedema.
^b The Angioedema Activity Score does not assess wheals (hives).

Table 3
Characteristics and availability of relevant patient-reported outcome measures in chronic urticaria

	UAS	AAS	UCT	CU-Q ₂ oL	AE-QoL
Original or source publication	⁴	²²	³⁹	⁴³	⁵²
Number of items (questions)	2 (everyday)	1–6 (everyday)	4 (once)	23 (once)	17 (once)
Recall period	1 d	1 d	4 wk	2 wk	4 wk
Applicable in CSU	+ ^a	+ ^b	+	+ ^a	+ ^b
Applicable in CIndU	–	+ ^b	+	–	+ ^b
Results available directly after administration (retrospective assessment)	–	–	+	+	+
Results available only in the future (prospective, diary-type assessment)	+	+	–	–	–
High level of patient compliance required	+	+	–	–	–
Scoring and evaluation fast and simple	+	+	+	–	–
Cutoff values published	–	–	+	–	–
Minimal important difference published	+	+	+	+	+

Cost-free use in routine patient management and investigator-initiated clinical research	+	+	+	+	+
Cost-free use in industry-driven projects and studies	+	–	–	–	–
Different language versions available ^f	+ ^c	+ ^d (German, American-English, Spanish, French, Portuguese, Azeri, Swedish, Hungarian, Romanian, Greek, Polish, Dutch, Russian, Canadian-French, Danish, Italian, Mexican, Japanese, UK-English, Canadian-English, Hebrew, Macedonian, Turkish, Brazilian-Portuguese)	+ ^d (German, American-English, Spanish, French, Turkish, Thai, Greek, Polish, Dutch, Russian, Canadian-English, Danish, Mexican, Portuguese, Brazilian-Portuguese, Finish)	+ ^e Italian, German, Greek, Spanish, Polish, Turkish, Persian, Thai	+ ^d (German, American-English, Spanish, French, Portuguese, Turkish, Azeri, Swedish, Hungarian, Hebrew, Romanian, Greek, Polish, Dutch, Russian, Canadian-English, Danish, Italian, Mexican, Japanese, Canadian-French, US-Spanish, Brazilian-Portuguese, Macedonian, Arabic (Jordan), Hebrew, Slovakian)

Abbreviations: AAS, Angioedema Activity Score; AE-QoL, Angioedema Quality of Life Questionnaire; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; UAS, Urticaria Activity Score; UCT, Urticaria Control Test.

^a Results may not provide an accurate picture in patients with CSU in whom recurrent angioedema is a major factor.

^b Applicable in those patients with CSU and CIndU who display recurrent angioedema, with or without wheals.

^c Availability in several languages. Original source is the urticaria guideline.⁴ Because of its easy structure, the Urticaria Activity Score is usually translated but not formally linguistically validated.

^d Availability may be checked at Moxie.³⁶

^e Availability may be checked at original author team.⁴³

^f Additional language versions may be or are in preparation (for more details with regard to the Angioedema Activity Score, Urticaria Control Test, and Angioedema Quality of Life Questionnaire versions, the corresponding author can be contacted).

in many clinical trials as an outcome parameter, including the recent studies on the efficacy and safety of omalizumab,^{14–18} when it once again demonstrated its high value and usefulness as a PRO measure.

The UAS focuses on 2 key symptoms of CSU, that is, wheals and itch. It is a diary-type tool that asks the patients once daily for numbers of wheals and severity of itch during the past 24 hours (Table 4). The answers related to each symptom are rated from 0 to 3 points, that is, the minimum and maximum daily score are 0 and 6 points, respectively, with higher values indicating stronger disease activity. Because of the considerable fluctuation of symptoms from day to day, data of at least 4 subsequent days should be collected to obtain a good picture of patients' current disease activity.¹⁹ In clinical studies and daily care it has been found most useful to collect and sum up the UAS from 7 days in a row (UAS7, range 0–42 points), which is now established and recommended by the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization's urticaria guideline (see Table 4).⁴

For the interpretation of PRO measure results, it is very important to know which score changes over time are really clinically meaningful to patients, that is, what is the minimal important difference (MID) (also known as minimal important change)? Currently, the MID of the guideline-recommended UAS7 is not known; but studies examining the MID are underway. In addition, it is important to know which scores represent mild, moderate, and severe disease activity. As of yet, there are no commonly accepted UAS7 score ranges or cutoff values available. In the recent phase III trials on omalizumab in CSU,^{14–18} a criterion for inclusion was a UAS7 of 16 points or greater during the baseline assessment; it has been promoted that a UAS7 less than 16 points indicates mild CSU, whereas a UAS7 of 16 points or greater indicates moderate to severe CSU. However, this cutoff value remains to be formally validated against appropriate anchors.

It may cause confusion that, during the past years, a different version of the UAS has been used in adults,²⁰ with different categories for wheal numbers (no wheals, 1–6 wheals, 7–12 wheals, >12 wheals) and a different frequency of documentation (twice daily instead of once daily).²⁰ For this UAS, an MID of around 10 points has been established.²⁰ At the time being, it is not fully clear how the scores of both UAS tools correspond to each other, which hampers the comparison and meta-analysis of studies that applied different UAS versions.

Table 4 Urticaria Activity Score		
Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals during last 24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals during last 24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals or large confluent areas of wheals during last 24 h)	Intense (severe pruritus that is sufficiently troublesome to interfere with normal daily activity or sleep)

Adapted from Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69(7):871; with permission.

In a recent randomized controlled trial on the efficacy and safety of the second-generation antihistamine rupatadine in chronic spontaneous urticaria, an additional children-adapted version of the UAS7 was applied. For this study, the guideline-recommended UAS was slightly modified by an adjusted documentation of wheal numbers to no wheals, 1 to 9 wheals, 10 to 30 wheals, and greater than 30 wheals, because of the lower body surface area of children.²¹ However, this UAS remains to be formally validated.

The major strength of the UAS7 is that it provides a fairly exact picture of the current frequency and severity of CSU symptoms because the short recall period of 24 hours for each entry and the summing up of 7 days in a row make sure that the provided information is accurate and fluctuations of the disease are leveled out. However, the UAS7 also has several limitations: (1) it only works prospectively, that is, results are not instantly available, for example, at a patient's first appointment; (2) it requires good patient compliance and documentation discipline (its results may become inaccurate or are lost in case patients forget to document their symptoms or forget to bring the documentation to the next appointment); (3) it only works in CSU but not patients with CIndU; (4) it is only validated for use in adults; (5) score ranges representing low, medium, or high disease activity have yet to be established; and finally (6) it does not include angioedema, although angioedema is a key symptom and major driver of disease burden in many patients. For these angioedema patients, different tools, such as the Angioedema Activity Score (AAS), are required. An overview of the characteristics and the availability of the UAS and other urticaria-relevant PRO measures is shown in [Table 3](#).

Angioedema Activity Score

The AAS has been developed as the first symptom-specific PRO measure to assess angioedema activity in patients with all forms of recurrent angioedema (RA).²² RA can be histamine mediated (in CSU and CIndU) or bradykinin mediated (RA due to C1-inhibitor deficiency and RA caused by intake of angiotensin-converting enzyme inhibitors).¹⁰

As the UAS, the AAS is a prospective, diary-type tool. It asks the patients to once daily document if angioedema occurred during the past 24 hours or not. If angioedema was present, the AAS asks 5 additional questions to determine the severity and impact of this episode, each with answer options that are scored from 0 to 3 points. Accordingly, the minimum and maximum daily score is 0 and 15 points. To get a sufficient picture of patients' disease activity, it is usually recommended to collect data from 4 weeks (AAS28).²² The AAS is particularly useful in patients with RA without wheals and in patients where angioedema is a predominant factor.

In its original validation study, the AAS was found to have a one-dimensional structure and excellent internal consistency.²² Its levels of validity and test-retest reliability were shown to be good.²² In addition, the AAS was demonstrated to be sensitive to changes of angioedema activity over time, and a MID of 8 points for the 7-day cumulative AAS (AAS7) is established.²² Finally, the AAS also has been applied successfully in recent randomized controlled trials in CSU²³ but also in RA due to C1-inhibitor deficiency.²⁴ The available language versions as well as their terms of use are shown in [Table 3](#).

Because the UAS and AAS are both diary-type tools with a comparable structure and scoring, their strengths and limitations are also comparable (see [Table 3](#)): As the UAS, the AAS provides an exact picture of the current frequency and severity of angioedema episodes; but, on the other hand, it also only works prospectively; ad hoc results are not available; AAS28 score ranges that can be regarded to represent

low, moderate, or high angioedema activity have yet to be established. However, the original validation study already provides information on AAS7 values of patients with different disease activities, that is, a mean AAS7 standard deviation of 6.5 ± 6.9 was found in patients with angioedema globally self-rating their disease activity as mild; a value of 15.4 ± 10.1 was found in patients indicating their angioedema activity to be moderate; a score of 21.2 ± 11.3 was determined in patients who reported their angioedema activity to be severe.²²

If the AAS is used in patients with CSU with wheals and angioedema, it should be made sure that patients do not confuse the two. Otherwise, the AAS results may not correctly capture angioedema-related disease activity.

CLINICAL MEASURES OF DISEASE ACTIVITY IN CHRONIC INDUCIBLE URTICARIAS

Cholinergic Urticaria Activity Score

In CIndUs, an assessment of the quality and quantity of symptoms alone does not provide a reliable picture of the patients' disease activity. As mentioned earlier, the avoidance behavior of patients with CIndU strongly influences the frequency and severity of their symptoms. Accordingly, in a PRO measure, the actual exposure to triggers would need to be evaluated as well. As of yet, the only CIndU for which such an activity score has been established is cholinergic urticaria. Here, the cholinergic UAS (CholUAS) has been developed and was found to be a valuable outcome parameter in a clinical trial.²⁵ The CholUAS is a modification of the UAS and collects data, once daily, on the intensity of wheals (not wheal numbers) and pruritus as well as the intensity of exposure to individually relevant symptom elicitors during the past 24 hours.²⁵ As in case of the UAS7, it makes sense to sum up 7 consecutive days in order to obtain a more reliable picture of the patients' current disease activity.

Critical Trigger Threshold Assessment

For CIndUs other than cholinergic urticaria, there are, as of yet, no comparable PRO tools available. However, the inducibility of symptoms opens up the possibility for an objective assessment of disease activity by determining CTTs. CTTs have also been found to be sensitive to changes, for example, during successful treatment.^{26–29} Examples for standardized CTT measurements are the assessment of the critical temperature threshold in patients with cold urticaria by using the Peltier-element-based TempTest,^{13,30–32} the standardized application of graded shear forces in symptomatic dermographism by using FricTest,^{33,34} or the standardized pulse-controlled ergometry provocation test in cholinergic urticaria.³⁵ For more details on available CTT test devices and measurement of CTTs in CIndUs, the authors would like to refer to the recent review of Magerl and colleagues.¹³

CLINICAL MEASURES OF DISEASE CONTROL

The treatment of CSU has improved strongly during the past years. The currently most widely accepted treatment algorithm suggests using second-generation antihistamines in the licensed dose as the first-line therapy, an up dosing of second-generation antihistamines to up to 4 times the licensed dose as second-line treatment, and the addition of omalizumab, cyclosporin, or montelukast as third-line options.⁴ However, most of these treatment options are off-label (up dosing of second-generation antihistamines, cyclosporin, montelukast), associated with an unfavorable long-term safety profile (cyclosporin), or go along with considerable costs (omalizumab). Accordingly, it is important that treatment decisions are made carefully and

that they are ideally based on and backed by a standardized, valid, and reliable documentation of the patients' current disease status.

Urticaria Control Test

The currently easiest way to assess the patients' disease status is to apply the Urticaria Control Test (UCT). The UCT was specifically developed and validated to determine disease control, in all forms of chronic urticaria (CSU and CIndU), that is, to determine the level of disease control but also to give a clear answer to the question of whether the urticaria is well-controlled or not, and thereby to aid and back treatment decisions. Several different language versions are available,^{36–39} and their terms of use are presented in [Table 3](#).

The UCT is a retrospective PRO measure with a recall period of 4 weeks that consists of only 4 questions. The answer options to each question are scored from 0 to 4 points and subsequently added up to the UCT score with a minimum and maximum value of 0 and 16 points, respectively. A score of 11 points or less points toward poorly controlled urticaria, whereas a score of 12 or higher indicates well-controlled disease.

The original publication of the UCT proved that the UCT strongly correlates with the UAS but also with the HR-QoL impairment in patients with chronic urticaria.³⁹ It was found to have good levels of validity, an excellent reliability, and a high screening accuracy to identify patients with insufficiently controlled disease.³⁹ The MID of the UCT was found to be 3 points in 2 independent studies^{38,40}; a change of a least 3 points can be regarded as a change that is meaningful to patients.

The major strengths of the UCT are its retrospective approach, short and simple structure, and its easy scoring system. It is possible to use the UCT at any patient presentation; its results are instantly available after completion; its clear cutoff value of 12 points enables a direct evaluation of the disease status. In addition, the UCT is applicable in all forms of chronic urticaria. These properties make the UCT an ideal PRO measure for daily patient management. However, one of its major strengths, its shortness, is also its limitation. Although UCT results are accurate, the information obtained by the UCT is not very detailed. If one wants to know exactly which symptoms currently occur and which areas of HR-QoL are impaired, the UCT is not a suitable tool to provide this information.

CLINICAL MEASURES OF HEALTH-RELATED QUALITY-OF-LIFE IMPAIRMENT

CSU causes major impairment of patients' HR-QoL^{5–7} for several reasons. The symptoms usually occur unpredictably and vary strongly with regard to their frequency and intensity. Accordingly, many patients have major problems planning their daily life. Symptoms, including chronic itch, often occur during the nights, and interference with sleep, difficulties concentrating during the next day, and a reduced ability to handle daily activities, including a reduced performance at work and school, are common. In addition, recurrent angioedema, which occurs in around 50% of patients with CSU with a preference of the face and upper respiratory tract,²³ commonly leads to disfigurement and fear of suffocation.

In order to better understand and assess the full extent of urticaria-related disease burden and/or its changes over time, it is not sufficient to just evaluate the frequency and severity of symptoms.⁴¹ For this purpose, disease-specific, patient-centered tools focusing on patients' HR-QoL are required. These tools should be preferred over generic HR-QoL instruments, unless a comparison of chronic urticaria with other disorders is intended because they are usually more robust and sensitive in obtaining meaningful QoL data⁴² as well as their changes over time.

Chronic Urticaria Quality of Life Questionnaire

The Chronic Urticaria Quality of Life Questionnaire (CU-Q₂oL) is the first disease-specific tool to assess HR-QoL impairment in patients with CSU.⁴³ It contains 23 questions and has a recall period of 2 weeks. Each question has 5 answer options that are scored from 0 to 4 points. The CU-Q₂oL may be applied as an index instrument to assess the overall CSU-related QoL impairment (total score assessment), but it may also be used to examine the profile of impairment by computing its domain scores. The total score is generated by summing up all 23 question scores and by subsequently transferring the score to a 0 to 100 scale to limit the influence of missing items.⁴³ Higher values indicate a higher HR-QoL impairment. The domain scores are computed similarly, with the exception that for each domain only the scores of that domain are considered.

Several language versions are available and have been validated.^{6,43–49} Although the CU-Q₂oL total score of all language versions is similarly computed and may be compared, the CU-Q₂oL domain structure varies between different versions, for example, between the original Italian version⁴³ and the German version,⁶ thus, limiting the possibility for comparisons or joint analyses of the domain scores.

In the original publication⁴³ and subsequent validation studies, the CU-Q₂oL has been found to have good levels of validity and reliability. In addition, a recent Korean study found a good sensitivity to change and suggested an MID of 15 points for the CU-Q₂oL total score.⁴⁷ Moreover, the CU-Q₂oL was found to be more sensitive in comparison with other, non-disease-specific HR-QoL measures, such as the Dermatology Quality of Life Index.⁵⁰ The CU-Q₂oL has been used in many clinical studies, including pharmacologic randomized controlled trials.^{15,23,51}

Major limitations of the CU-Q₂oL are (1) that it is only applicable in CSU but not in CIndUs (CIndUs disease-specific HR-QoL measures are not available yet and strongly needed); (2) that good information on which CU-Q₂oL scores indicate mild, moderate, and severe HR-QoL impairment are missing (however, studies to determine this are currently underway); (3) that because of the relatively complicated scoring system, the CU-Q₂oL is not ideally suited for routine patient management (here only a rough estimation of the total score is realistic rather than an exact evaluation of the total and all domain scores); and (4) that the CU-Q₂oL questions are not well tailored for patients with CSU predominantly with angioedema (although angioedema is part of the CU-Q₂oL symptoms domain). For the last limitation, the Angioedema Quality of Life Questionnaire (AE-QoL) was developed.

Angioedema Quality of Life Questionnaire

The AE-QoL is the first symptom-specific PRO measure to assess HR-QoL in RA.⁵² As the AAS, it is applicable for all subforms of RA and has a recall period of 4 weeks.⁵² With regard to its characteristics, structure, and scoring, the AE-QoL is closely related to the CU-Q₂oL. It consists of 17 questions with 5 answer options each that are all scored from 0 to 4 points.

In the original publication on its development and validation, the AE-QoL has been found to have a 4-dimensional structure with good levels of internal consistency as well as a valid total score.⁵² The question scores can be summed up to a total score but also grouped together to 4 different domain scores (functioning, fatigue/mood, fears/shame, food), which are each displayed on a 0 to 100 scale.⁵² Accordingly, the AE-QoL may serve as an index or a profile instrument for RA-related QoL impairment.

In addition to the original publication, in a recent study, the authors were able to confirm the good convergent validity of the AE-QoL: they found its total scores to

correlate well with the frequency of angioedema attacks, that is, to be higher in patients with higher frequency of attacks. In addition, the authors were able to prove the AE-QoL's sensitivity to change as well as to determine its MID, which is 6 points.⁵³

Although only published in 2012, the AE-QoL is available in many different language versions already (see [Table 3](#)) and has been applied in different randomized controlled clinical trials in CSU and hereditary angioedema with good results.^{23,24}

Major limitations of the AE-QoL are comparable with those of the CU-Q2oL: (1) it has relatively complicated scoring system, which may hamper its broad application in routine patient management; (2) in patients with CSU or CIndU with wheals and angioedema, it provides only a picture of the angioedema-related component of HR-QoL impairment; and (3) it will not yield accurate results in patients with CSU who confuse wheals and angioedema.

In addition to the CU-Q2oL and the AE-QoL, there is a tool available to assess HR-QoL in patients with chronic itch, the ItchyQoL.^{11,54} This PRO instrument is particularly interesting for physicians and researchers who want to focus specifically on pruritus and its impact.



Fig. 1. How PROs can be embedded into routine patient management.

SUMMARY

The use of standardized, valid, and reliable clinical measures is an important component of modern patient-centered care. In addition, the availability of these measures is essential for the quality and performance of clinical trials.

In the last years, several new and well-developed clinical measures became available in CSU and ClndUs, that is, PRO instruments to determine disease activity, disease control, and HR-QoL impairment as well as CTT test devices. These measures strongly improved the understanding, assessment, and evaluation of these disorders. Some even became approachable by studies for the first time.

In routine patient management, the presented clinical measures can help aid and back treatment decisions, provide better insights into the patients' disease burden, and facilitate, improve, and standardize the increasingly important documentation work. In addition, clinical measures may serve to better determine changes in patients' disease status over time. This is particularly relevant in times of both limited resources and high costs for modern treatment options, which require careful decisions on the best individual therapy approaches.

The clinical measures described in this review have already proven their high value in daily patient care and clinical studies. Most of them are self-explaining, easy to administer, and simple to score and evaluate. If well embedded into daily routines (Fig. 1), they may help save valuable time for a longer and more intensive communication with patients because an important part of the required documentation work is done by those who are the center of our efforts, the patients themselves.

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