


## ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

## Development of the Cold Urticaria Activity Score

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**Abstract**

**Background:** Cold urticaria (ColdU) is a form of inducible urticaria where cold induces wheals and/or angioedema. The burden of disease is high and linked to trigger thresholds, exposure, and avoidance. There are presently no validated patient-reported outcome measures (PROMs) to assess and monitor disease activity. Our objective was to develop a disease-specific activity score for ColdU that is easy to administer and evaluate.

**Methods:** A Cold Urticaria Activity Score (ColdUAS) questionnaire was developed, directed by PROM developing guidelines. After the generation of a conceptual framework, the item generation phase included the literature research on ColdU signs and symptoms and on comparable tools for similar diseases and 47 ColdU patient interviews. Subsequently, an impact analysis for content validity was performed. The final selection of items underwent expert review for face validity and cognitive debriefing.

**Results:** The ColdUAS, a self-administered questionnaire for the prospective assessment of disease activity in patients with ColdU, consists of 4 items: 1. the frequency and severity of the signs (wheals and/or angioedema), 2. the frequency and severity of the symptoms (e.g., itch and burn), 3. the exposure to specific triggers, and 4. the avoidance of these triggers. The recall period for each item is the last 24 h.

**Conclusions:** The ColdUAS is the first disease-specific PROM to assess ColdU disease activity. It may help to better assess patients' disease status in routine clinical practice as well as in clinical trials. Anchor-based approaches are currently used to validate the ColdUAS.

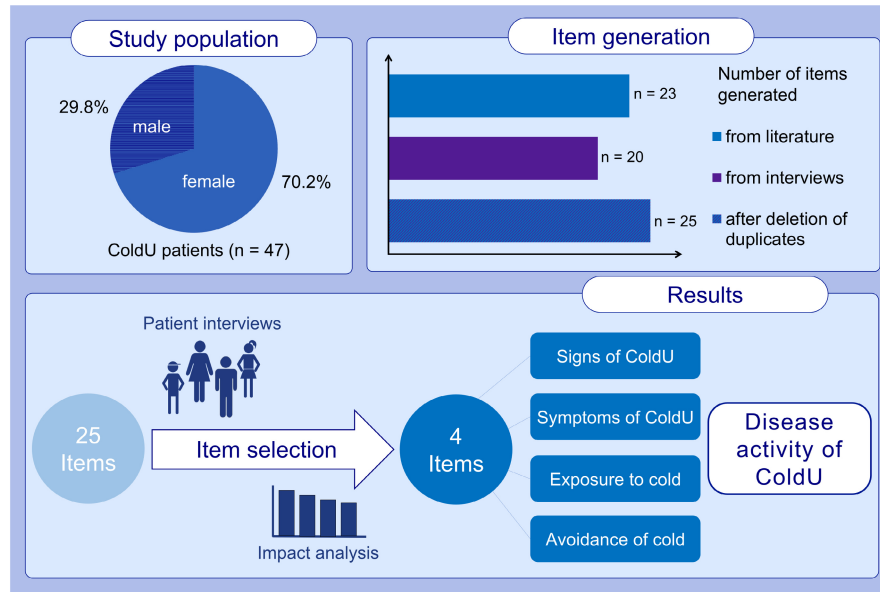
**KEYWORDS**

chronic inducible urticaria, cold urticaria, disease activity, patient-reported outcome measures, urticaria activity score

**Abbreviations:** CholUAS, Cholinergic Urticaria Activity Score; ColdU, cold urticaria; ColdUAS, Cold Urticaria Activity Score; CST(s), cold stimulation test(s); CSU, chronic spontaneous urticaria; CTT, critical temperature threshold; ICT, ice cube test; PROM, patient-reported outcome measure; UAS, Urticaria Activity Score.

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## GRAPHICAL ABSTRACT

The ColdUAS development process was directed by PROM guidelines. For item generation 47 interviews with ColdU patients and a comprehensive literature research was performed. By conducting an impact analysis, cognitive debriefings, and an expert review final items were selected. The 4-item ColdUAS is the first self-administered questionnaire for the prospective assessment of disease activity in ColdU patients.

Abbreviations: ColdU, Cold urticaria; ColdUAS, Cold Urticaria Activity Score; PROM, patient-reported outcome measures

## 1 | BACKGROUND

Cold urticaria (ColdU) is an inducible urticaria where skin exposure to cold temperatures results in wheals, angioedema, or both. Most cases of ColdU are chronic, that is, longer than 6 weeks, with an average duration of 6 years.<sup>1-3</sup> ColdU is the second most common chronic inducible urticaria, with an incidence in the general population of approximately 0.05% globally and a higher prevalence in northern countries.<sup>4,5</sup>

The signs and symptoms of ColdU usually appear a few minutes after cold exposure, upon rewarming of the skin.<sup>1,6</sup> Trigger factors include cold liquids, cold objects, and cold air, which can be affected by co-factors such as humidity and wind.<sup>6,7</sup> The spectrum of reactions to these triggers varies widely, ranging from mild localized whealing to dangerous generalized and systemic reactions and potentially life-threatening angioedema.<sup>3,8,9</sup> About 40% of ColdU patients develop systemic reactions, such as vertigo, nausea, hypotension, dyspnea, or anaphylaxis, in addition to wheals or angioedema.<sup>8,10</sup> Many ColdU patients experience a severe impairment in their quality of life, as they frequently avoid outdoor activities or contact with cold water, such as swimming<sup>11</sup> but can also experience symptoms in daily activities such as preparation of cold food, wet cleaning, and skin contact with cool objects, for example, toilet seats.

Cold urticaria is classified as typical or atypical, as well as primary or secondary.<sup>2</sup> Typical ColdU is diagnosed by a positive standardized cold stimulation test (CST), performed with an ice cube or TempTest®.<sup>1,2</sup> By contrast, atypical ColdUs are characterized

by either negative results or atypical responses to standardized CSTs.<sup>2,3,10</sup> ColdU is classified as primary in the absence of an underlying disease. In secondary forms, an underlying disease can be identified, for example, hematological or autoimmune disorders.<sup>1,6,12</sup>

As of today, H1 antihistamines are the first-line therapy and the only licensed treatment option for ColdU patients.<sup>2</sup> Less than 50% of ColdU patients achieve complete disease control with approved or upused antihistaminic treatment.<sup>2,13,14</sup> Omalizumab can be effective in antihistamine-refractory ColdU. However, omalizumab is not licensed for ColdU, and not all patients benefit sufficiently.<sup>2,14</sup> Thus, the overall care situation is not satisfactory and shows a great need for new therapies.

When developing new therapies, it is essential to be able to assess disease activity and its change to treatment.<sup>15</sup> Likewise, in routine care, monitoring therapy responses in the patient's daily life can help improving patient care.

However, at present, there are no validated disease-specific patient-reported outcome measures (PROMs) to assess and score disease activity in ColdU patients. PROMs are a standardized method of assessing a patient's health status, record the unfiltered patient perspective on their disease, and prevent a loss of important information that may occur in the case of isolated evaluations by physicians.<sup>16,17</sup>

Cold urticaria is a distinct clinical entity and different in its triggers of signs and symptoms, clinical manifestations, and course and response to treatment from other diseases including other types of urticaria. Existing tools for the assessment of disease activity, such

as the Urticaria Activity Score (UAS) for chronic spontaneous urticaria (CSU), cannot be used for ColdU, since ColdU patients may have high disease activity but only mild signs and symptoms because of strong cold avoidance behavior.<sup>18</sup> Accordingly, the actual exposure to trigger temperatures and the avoidance behavior need to be included in a disease activity assessment. Subsequently, the aim of this study was to develop a disease-specific PROM for assessing disease activity in ColdU patients.

## 2 | PATIENTS AND METHODS

The development of the Cold Urticaria Activity Score (ColdUAS) was divided into three major phases: 1. conceptual framework development, 2. item generation, and 3. item selection. An overview of the process is depicted in [Figure 1](#).

### 2.1 | Conceptual framework

As a first step, a conceptual framework was generated to base the item generation process. The ColdUAS core development group (Dorothea Terhorst-Molawi, Karsten Weller, Sabine Altrichter, Marcus Maurer) defined the conceptual framework and screened similar disease activity scores for content, structure, and scoring systems. Furthermore, the minimal number of required patient interviews per developmental stage was defined. Because of the expected wide range of symptom expression and severity, we aimed to assess at least 30 patients by semi-structured interviews.

### 2.2 | ColdUAS item generation

Item generation was performed by following three steps: a literature research to identify all relevant symptoms and triggers of cold reactions (1), semi-structured interviews with 47 ColdU patients (2) and an expert review to add potentially relevant items (3).

#### 2.2.1 | Literature research

On August 30, 2019, we conducted a literature research in the electronic database PubMed with the terms ("*cold urticaria*" AND *symptoms*) OR ("*cold urticaria*" AND *triggers*). Relevant public data published between 1961 and 2019 in German and English with full text available were included for further screening, and references in key publications were cross-checked. All included publications and generated items are summarized in [Table 1](#).

In addition, comparable instruments and activity scores were sought in PubMed using mesh terms ("*urticaria activity score*" AND (*development* OR *validation*)) OR ("*angioedema activity score*" AND (*development* OR *validation*)). Information on comparable tools can be retrieved from supplementary file [Table S1](#).

#### 2.2.2 | Semi-structured patient interviews for item generation

We performed semi-structured interviews of about 60 min duration each with 47 ColdU patients recruited at the Urticaria

**FIGURE 1** After the development of a conceptual framework for the ColdUAS, 25 potentially relevant items were generated. Subsequently cognitive debriefing, an impact analysis and an expert review for face validity were performed during the item selection process and resulted in a final set of 4 questions. The final 4-item ColdUAS is user-friendly and suited for clinical trials and daily routine care. ColdUAS, Cold Urticaria Activity Score; ColdU, Cold urticaria

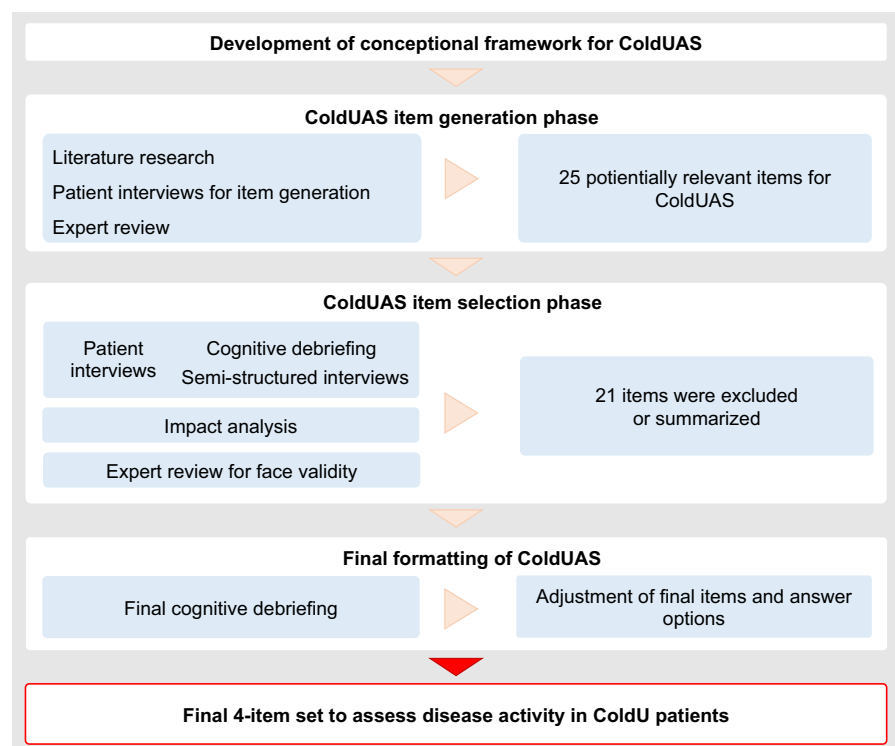


TABLE 1 Results of item generation and item selection process

Source	Items generation	Item selection/modifications
8,15,38-45 & PI (97.9%)	Erythema	Frequency and severity of signs of ColdU
1,6,8,15,28,38-51 & PI (78.7%)	Wheals	
1,6,8,28,38,39,42,47-50 & PI (57.5%)	Angioedema	
PI (38.3%)	Acral swelling	
1,8,15,28,38-40,42,43,50 & PI (97.9%)	Pruritus	Frequency and severity of symptoms of ColdU
1,6,9,28,42,49-51 & PI (27.7%)	Systemic reaction/hypotension	
1,8,49 & PI (0%)	Tachycardia	
1,6,49 & PI (4.3%)	Anaphylaxis	
1,8,39,50 & PI (4.3%)	Syncope	
8,39,40 & PI (27.7%)	Vertigo	
1,6,8,40,49,51 & PI (14.9%)	Dyspnea	
6,8,51 & PI (0%)	Conjunctive hyperemia/rhinorrhea	
1,8 & PI (2.1%)	Nausea	
1,8,42,47,50 & PI (6.4%)	Gastrointestinal symptoms	
51 & PI (0%)	Muscle weakness	
8 & PI (0%)	Fatigue	
6,9,41 & PI (8.5%)	Pain	
PI (2.1%)	Feeling hot/flush	
1,6,15,28,38-50 & PI (91.5%)	Cold temperatures	
1,6,9,38-40,42,43,45-51 & PI (80.5%)	Cold water	
1,6,15,39,42,45,49 & PI (82.9%)	Cold objects	
1,6,39,42,47 & PI (19.2%)	Ingestion of cold food/beverage	
1,28,38,39,43,44,50 & PI (76.6%)	Outdoor activities	
1 & PI (0%)	Friction	
1,6,9,28,49 & PI (100%)	Avoidance of triggers	Avoidance behavior with regard to specific triggers of ColdU

Note: Table 1 shows all 25 items generated from literature research and patient interviews (PI,  $n = 47$ ). The percentage in brackets shows the number of patients who reported the sign/symptom/trigger/avoidance described. All of the listed items were confirmed as clinically relevant by the expert group.

$n\%$  of patients reported corresponding item in patient interview.

Abbreviations: ColdU, cold urticaria; PI, patient interview.

Center of Reference and Excellence (UCARE) at Charité—Universitätsmedizin Berlin, Germany between July 2019 and July 2020. Our study was approved by the local ethics committee (reference EA1/385/13 & EA1/398/20), and all patients provided written informed consent. Eligible for inclusion were patients aged 12 years and older with any form of cold urticaria. At the timepoint of interview, the patients had active disease and could be on treatment for their ColdU. All patients underwent two cold provocation tests: a standardized ice cube test (ICT) and a standardized assessment of the critical temperature threshold (CTT) with TempTest®. The CTT indicates the warmest temperature at which a ColdU patient develops wheals.<sup>19,20</sup>

Most of the ColdU patients were women ( $n = 33$ , 70.2%), and 34 and 13 patients had typical and atypical ColdU, respectively. 3 minors (14–17 years old) were included. All patients with typical ColdU had positive test results (wheals) to ICT and/or TempTest®. Patients with atypical cold urticaria forms were diagnosed based on modified provocation tests and/or history and photodocumentation. The clinical characteristics of the patient population are presented in Table 2 (more information in Figure S1).

### 2.2.3 | Expert review

The results of the literature search and the transcribed semi-structured patient interviews were reviewed by the ColdUAS core development group. Common main symptoms, triggers, and avoidance behavior of ColdU patients were selected for the formulation of questions.

## 2.3 | ColdUAS item selection

The item selection was completed in 3 steps: 1. patient interviews, 2. impact analysis, 3. expert review.

### 2.3.1 | Patient interviews for item selection

For the selection of final items, a content validity analysis of each item was performed. Comprehensibility was assessed by methods of cognitive debriefing in 10 patients according to PROM guidelines.<sup>16</sup> Patients were asked whether they could easily read and

**TABLE 2** Demographic characteristics of 47 ColdU patients for item generation and 27 patients for item selection included at Charité Berlin between July 2019 and July 2020

	ColdUAS item generation phase			ColdUAS item selection phase		
	All patients	Typical ColdU	Atypical ColdU	All patients	Typical ColdU	Atypical ColdU
Patient, <i>n</i>	47	34	13	27	20	7
Gender						
Female, <i>n</i> (%)	33 (70.2%)	22 (64.7%)	11 (84.6%)	19 (70.4%)	14 (70%)	5 (71.4%)
Male, <i>n</i> (%)	14 (29.8%)	12 (35.3%)	2 (15.4%)	8 (29.6%)	6 (30%)	2 (28.6%)
Age, years, median [min, max]	39 [14, 82]	42.5 [14, 82]	31 [16, 66]	38 [14, 67]	39.5 [14, 67]	31 [18, 66]
Age of disease onset, years, median [min, max]	29 [0, 81]	31.5 [0, 81]	16 [10, 41]	28 [0, 64]	30.5 [0, 64]	22 [41, 10]
Disease duration, months, median [min, max]	72 [3, 600]	48.5 [3, 576]	120 [23, 600]	60 [4600]	48.5 [4, 576]	108 [9, 600]
Cold-induced reactions in the last 12 months						
Pruritus	46 (97.9%)	34 (100%)	12 (92.3%)	27 (100%)	20 (100%)	7 (100%)
Wheals	37 (78.7%)	27 (79.4%)	10 (76.9%)	23 (85.2%)	16 (80%)	7 (100%)
Angioedema	27 (57.5%)	19 (55.9%)	8 (61.5%)	14 (51.9%)	11 (55%)	3 (42.9%)
Acral swelling	18 (38.3%)	13 (38.2%)	5 (38.5%)	9 (33.3%)	7 (35%)	2 (28.6%)
Gastrointestinal symptoms	3 (6.4%)	2 (5.9%)	1 (7.7%)	1 (3.7%)	1 (5%)	0
Dyspnea	7 (14.9%)	5 (14.7%)	2 (15.4%)	5 (18.5%)	3 (15%)	2 (28.6%)
Hypotensive symptoms <sup>a</sup>	13 (27.7%)	10 (29.4%)	3 (23.1%)	10 (37%)	8 (40%)	2 (28.6%)
Measured hypotension <sup>b</sup> and/or loss of consciousness (anaphylactic shock)	2 (4.3%)	1 (2.9%)	1 (7.7%)	2 (7.4%)	1 (5%)	1 (14.3%)
Nausea	1 (2.1%)	0	1 (7.7%)	1 (3.7%)	0	1 (14.3%)
Feeling hot/flush/burning sensation	1 (2.1%)	1 (2.9%)	0	1 (3.7%)	1 (5%)	0
Pain	4 (8.5%)	2 (5.9%)	2 (15.4%)	2 (7.4%)	2 (10%)	0
Cold stimulation tests						
Ice Cube Test positive	32 (68.1%)	31 (91.2%)	0	18 (66.7%)	18 (90%)	0
TempTest <sup>®</sup> positive	31 (65.9%)	31 (91.2%)	0	20 (74.1%)	20 (100%)	0
CTT median [min, max]	18 [7, 27]	18 [7, 27]	-	19.5 [7, 27]	19.5 [7, 27]	-

Abbreviations: ColdU, cold urticaria; ColdUAS, Cold Urticaria Activity Score; CTT, critical temperature threshold.

<sup>a</sup>e.g., dizziness, sensation of fainting.

<sup>b</sup>Measured hypotension: blood pressure <90/60 mmHg.

understand each question, response options, and given instructions. Furthermore, all patients had to paraphrase each item in order to test comprehensibility.

In addition, we performed semi-structured interviews with 25 ColdU patients to verify comprehensiveness. To this end, patients were asked whether anything was missing and whether they had further suggestions on the structure and content of the activity score.

This step helped to decide whether an item would remain or be dropped from the questionnaire.

### 2.3.2 | Impact analysis

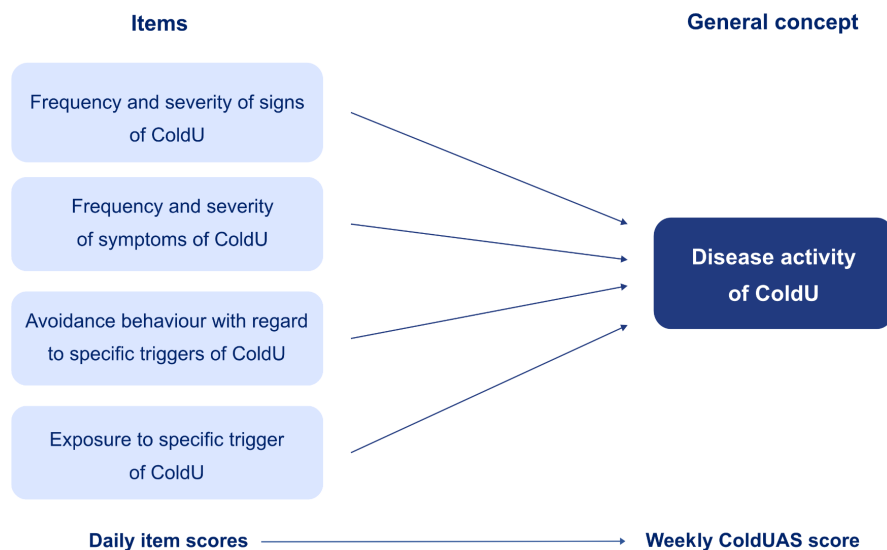
An impact analysis was performed to assess the frequency and importance of each item within the content validity analysis and to exclude all potential ColdUAS items with a low impact.

For the impact analysis, 27 ColdU patients evaluated the importance of each item on a 5-point scale (1 = not important to 5 = extremely important) and specified whether they had experienced the item content within the last year (frequency; yes = 1; no = 0). The “frequency” of each item was calculated as the percentage of patients who indicated that they experienced the item content within the last year. The impact score was calculated as product of frequency and mean importance of each item.

### 2.3.3 | Expert review for face validity and ColdUAS comprehension

After completing the content validity assessment, the expert group reviewed all items. The face validity assessment proposed an “impact” score of 3 points as the best suitable cutoff value for item

## ColdUAS – Cold Urticaria Activity Score



**FIGURE 2** Conceptual framework of ColdUAS. The final 4-item set results in the assessment of disease activity of ColdU. ColdUAS, Cold Urticaria Activity Score; ColdU, Cold urticaria

selection. All questions and answer options were modified for easier comprehension according to patients' feedback from the cognitive debriefings ( $n = 10$ ) and semi-structured interviews ( $n = 25$ ).

## 2.4 | Final formatting of the ColdUAS

After the item selection phase was completed, the final items to be used for the ColdUAS validation study were chosen. Five questions were added as anchor questions for later validation. Furthermore, an instruction section was developed by the expert group to introduce patients to the questionnaire and provide guidance on how to complete it. The form of the ColdUAS was updated in regard to the final item set, the requirements of the validation study and the documentation period of 14 days. Subsequently, a cognitive debriefing of the final version was performed with 7 ColdU patients aiming to confirm the comprehensiveness and comprehensibility of each item and answer option.

## 2.5 | Development of an US American-English version

The US American-English version was developed by two independent translators who are bilingual in the source language German and English. Both forward translators were naïve on the construct measured by the ColdUAS. The two forward translations were reviewed and adjusted by a US American-English native speaker and urticaria expert in cooperation with the ColdUAS core development group. A backward translation was then generated by a German native speaker, compared with the English translation and finally tested for congruence.

At last, a final US American-English version was created after consensus with the ColdUAS developers and underwent cognitive debriefing with 9 US American-English native speaking ColdU patients (4 female, 5 male, median age: 34.5, range: 22–49).

## 2.6 | Data assessment and statistical analysis

Semi-structured interviews were documented using Microsoft Word (version 16.52 [21080801]). For descriptive statistical analyses, Microsoft Excel (version 16.49 [21050901]) was used. Linear variables are given as median (and range), binominal variables as percentage.

## 3 | RESULTS

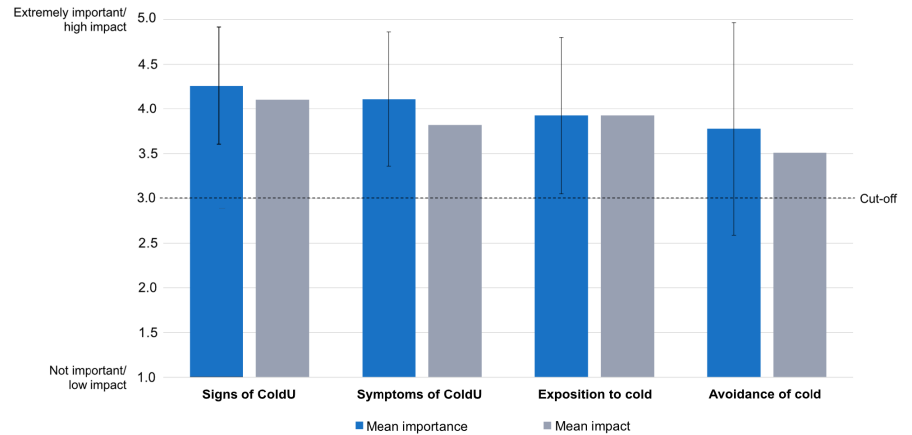
### 3.1 | Conceptual framework

In the conceptual framework (Figure 2), ColdU disease activity was defined as the frequency and severity of signs and symptoms of ColdU over a certain period of time (the documentation period). The exposure to typical triggers of ColdU as well as their avoidance should be considered as influencing factor for the assessment of disease activity. The main purpose of the ColdUAS was defined to a) determine disease activity during the documentation period and b) determine changes in disease activity over time, for example, before and after treatment adjustment. The target group of the ColdUAS was defined as all patients with typical or atypical ColdU aged 12 years and older, including secondary and familial ColdU. The type of assessment done with the ColdUAS was defined as a diary-type tool to record the current activity on a daily basis (recall period =24 h) for 1 week or longer.

### 3.2 | ColdUAS item generation

As a result of the literature research, patient interviews and expert input, a total of 25 potential items were put forward for inclusion in the ColdUAS (Table 1). The literature research identified the most frequent symptoms and triggers of ColdU as well as existing activity scores.<sup>21–23</sup>

**FIGURE 3** Impact score of each item was calculated from the product of frequency (percentage of patients who experienced the item content within the last year) and mean importance (1 = not important to 5 = extremely important) of all patients ( $n = 27$ ). The impact analysis showed a high impact for all 4 tested items with a cut-off value of 3 (median: 3.87; range: 3.51–4.11  $\pm$  SD: 0.25)



During semi-structured interviews all patients were asked about their ColdU symptoms, triggers, co-factors to cold exposition, secondary diagnoses, and medication use. All patients reported to have experienced wheals and/or angioedema and/or acral swelling due to cold. Virtually all patients (97.9%) had experienced itching, whereas 8.6% reported local pain caused by cold exposure. Around half of the patients had a history of systemic symptoms including vertigo, hypotension, and dyspnea.

The expert group reviewed all generated items and similar tools to assess disease activity (Table S1).<sup>21–23</sup> The Cholinergic Urticaria Activity Score (CholUAS)<sup>23</sup> was used as a model for the ColdUAS, as it also includes trigger factors when assessing disease activity. After expert discussion and evaluation of generated items and pre-existing disease activity tools, all items were condensed to 4 questions that cover all aspects of patient interviews and literature review, resulting in a preliminary version of the ColdUAS (Figure S2).

### 3.3 | ColdUAS item selection

#### 3.3.1 | Patient interviews for item selection

The preliminary version of the ColdUAS was tested during a first cognitive debriefing with 10 patients for content validity (10 females; median age: 40; range: 14–77). Eight patients showed no difficulty in comprehension. Furthermore, all patients were able to paraphrase the individual questions and response options. Two patients had problems to work with the grading of the answers. Subsequently, the wording of the response options and the instruction section were adjusted in the final version.

Furthermore, an evaluation of the preliminary questionnaire was performed by 25 of 27 ColdU patients from the item selection phase: for 22 patients, all questions were well understandable. Five patients reported to have problems in understanding the answer option “what?,” which was a free text field in the preliminary version and was removed after an expert review for the final version. In addition, patients gave their feedback on the original documentation period of 1 week stating that the time period is too short. Furthermore, the following missing items were mentioned:

1. A field for therapy. This was added, as a result, to the instruction section of the ColdUAS. It is not part of the ColdUAS but can capture additional information.
2. Space to include temperature or weather information. This point was discussed within the expert group, and it was agreed that the item on exposure covers this point.
3. Two patients proposed to add a free text field for special activities within the documentation period. After discussion, the expert group decided not to include this to keep the questionnaire as simple and easy to analyze as possible.

All comments were discussed by the expert group at the end of the item selection phase (Table S2).

#### 3.3.2 | Impact analysis

The impact analysis was performed to identify items that were not important and to confirm the relevance of the developed items. A total of 27 patients (19 females; 8 males, median age: 38 range: 14–67, 3 patients <18 y/o) took part in the impact analysis. The median duration of disease was 60 months, and 20 and 7 patients had typical and atypical ColdU, respectively (Table 2).

For item selection, the impact of each item was computed. The impact analysis showed a high impact for all 4 tested items (median: 3.87; range: 3.51–4.11  $\pm$  SD: 0.25) (Figure 3). Since the impact score of all items was found to be high, that is, higher than 3, the expert group decided to include all tested items in the final version.

Through the assessment of each item and its comprehensibility, we concluded that every item is important to be part of the questionnaire, and no further item reduction was performed.

#### 3.3.3 | Expert review and final formatting of the ColdUAS

The final item responses were designed as a 4-point Likert scale with answer options “No,” “mild,” “moderate,” “severe” (for question 1–3) and answer options “No,” “partially,” and “completely”

for question 4. The format and design of the ranking scale were selected to best represent symptom severity and triggers without losing important information when considering disease activity. Another reason for the decision to use a 4-point Likert scale was that other established dermatological and urticaria activity scores already showed a good assessment of disease activity and valid outcome measures.<sup>21–23</sup>

Based on patient interviews, cognitive debriefing, and expert input, the documentation period was defined to be 2 weeks. Nevertheless, during the patient interviews it was found that the desired documentation period was between 1 and 4 weeks. After expert review, it was agreed that a survey period of 2 weeks should be sufficient. However, it was decided to evaluate the most sufficient documentation period during the validation phase and define the final documentation period after validation is completed.

During a second cognitive debriefing with the final ColdUAS, there were no difficulties in understanding the instruction section, items, and answer options as well as no requests for changes by the patients ( $n = 7$ ; 7 females; median age: 49 years; range: 16–78). This development process resulted in the generation of the 4-item ColdUAS (Figure 4A). Furthermore, we generated a US American-English version of the ColdUAS (Figure 4B), which was developed based on a structured translation process.

## 4 | DISCUSSION AND CONCLUSION

As of now, there are no validated PROMs for the assessment of ColdU. Following PROM-development guidelines,<sup>16</sup> we developed the first disease-specific diary-type instrument, the ColdUAS, to measure disease activity in patients with ColdU. The ColdUAS can be used by patients who are at least 12 years old and have any form of ColdU, that is, typical or atypical ColdU, including primary, secondary, and familial subtypes.

The UAS for CSU has been proven to be a valid outcome measure.<sup>21</sup> It is recommended for the use in CSU by the current international EAACI/GA<sup>2</sup>LEN/EuroGuiDerm/APAAACI urticaria guideline.<sup>24</sup> However, its use is not appropriate for ColdU and other CIndUs, where specific and definite trigger factors as well as their avoidance play a major role and affect the occurrence of signs and symptoms. Other comparable disease activity scores that were evaluated during the development of the ColdUAS include the Angioedema Activity Score (AAS)<sup>25</sup> and the Cholinergic Urticaria Activity Score (CholUAS).<sup>23</sup> The AAS is a validated tool to assess disease activity in patients with recurrent angioedema.<sup>26</sup> Although patients with ColdU can develop angioedema, the use of the AAS for ColdU is not appropriate. Like the UAS, it does not assess trigger exposure or avoidance, which affect patients' symptom burden and disease activity. The CholUAS,<sup>23</sup> which is

**(A) Kälteurtikaria-Aktivitätsscore**

**Basisinformationen**

Name: \_\_\_\_\_

Geschlecht:  weiblich  männlich  divers

Geburtsdatum: \_\_\_\_ . \_\_\_\_ . \_\_\_\_

Aktuelle Medikation: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Anleitung**

Sie leiden unter einer Kälteurtikaria. Mit den folgenden Fragen soll die Krankheitsaktivität ihrer Kälteurtikaria über einen Zeitraum von 14 Tagen erfasst werden.

Bitte beantworten Sie dazu *einmal täglich* die folgenden Fragen in der jeweiligen Spalte. Beantworten Sie die Fragen immer ungefähr zur gleichen Tageszeit. Beziehen Sie sich bei den Antworten immer auf die *letzten 24 Stunden*.

Bitte lesen Sie sich jede Frage sorgfältig durch und wählen Sie aus den Antwortmöglichkeiten diejenige aus, die für Sie *am besten* zutrifft. Wählen Sie bitte immer *nur eine Antwortmöglichkeit* für jede Frage. Bitte machen Sie das jeden Tag und bitte beantworten Sie alle Fragen jeden Tag.

Woche 1: von ____/____/____ bis ____/____/____	Tag 1	Tag 2	Tag 3	Tag 4	Tag 5	Tag 6	Tag 7
1. Hatten Sie in den letzten 24 Stunden durch Kälte ausgelöste Quaddeln oder Schwellungen?	Nein	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, leichte Quaddeln oder Schwellungen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, mittelstarke Quaddeln oder Schwellungen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, starke Quaddeln oder Schwellungen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Hatten Sie in den letzten 24 Stunden durch Kälte ausgelösten Juckreiz, Brennen, Schmerzen oder Hitzegefühl?	Nein	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, leichten Juckreiz, Brennen, Schmerzen oder Hitzegefühl	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, mittelstarken Juckreiz, Brennen, Schmerzen oder Hitzegefühl	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, starken Juckreiz, Brennen, Schmerzen oder Hitzegefühl	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Waren Sie in den letzten 24 Stunden Kälte ausgesetzt, die üblicherweise Kälteurtikariabeschwerden auslöst?	Nein	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, Kälte, die üblicherweise leichte Beschwerden auslöst	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, Kälte, die üblicherweise mittelstarke Beschwerden auslöst	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, Kälte, die üblicherweise starke Beschwerden auslöst	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Haben Sie in den letzten 24 Stunden Kälte gemieden, die üblicherweise zu Kälteurtikariabeschwerden führt?	Nein	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, teilweise gemieden	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ja, vollständig gemieden	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**(B) Cold Urticaria Activity Score**

**Basic information**

Name: \_\_\_\_\_

Gender:  female  male  divers

Date of birth: \_\_\_\_ . \_\_\_\_ . \_\_\_\_

Cold urticaria onset (month/year): \_\_\_\_ / \_\_\_\_

Current medication: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Instructions**

You have cold urticaria. The following questions are intended to record the disease activity of your cold urticaria over a 14-day period.

Please answer the following questions in the respective column once a day. Always answer the questions at about the same time of day. Always refer to the previous 24 hours.

Please read each question carefully and choose the response that applies best to you from the possible answers. Please choose *only one answer* for each question. Please answer all questions according to these instructions every day.

Week 1: from ____/____/____ to ____/____/____	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. In the past 24 hours, have you had wheals or a swelling episode caused by cold?	No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, mild wheals or swelling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, moderate wheals or swelling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, severe wheals or swelling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. In the past 24 hours, did you experience itching, burning, pain, or feeling hot because of cold exposure?	No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, mild itching, burning, pain or feeling hot	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, moderate itching, burning, pain or feeling hot	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, severe itching, burning, pain or feeling hot	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. In the past 24 hours, have you been exposed to cold temperatures that usually cause cold urticaria symptoms?	No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, cold, which usually causes mild symptoms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, cold, which usually causes moderate symptoms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, cold, which usually causes severe symptoms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. In the past 24 hours, have you avoided cold temperatures that usually lead to cold urticaria symptoms?	No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, partially avoided	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes, completely avoided	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

FIGURE 4 (A) ColdUAS—German version (B) ColdUAS—US American-English version

currently undergoing validation, served as a model in the development of a ColdUAS, as it considers trigger factors and measures symptom intensity using a Likert scale (Table S1). What the ColdUAS shares with the UAS, the AAS and the CholUAS, are its low item number and the diary-type design.<sup>21,23,25</sup> The ColdUAS consists of only 4 items, which makes it a simple tool for the daily use by patients.

Our impact analysis showed that all 4 ColdUAS items are important for assessing disease activity during one or more weeks. The UAS has a minimum assessment period of 4 days<sup>27</sup> and is typically used on 7 consecutive days to determine disease activity during 1 week (UAS7).<sup>21</sup> The AAS is most often used for 28 consecutive days (AAS28) but can also be used for 1 week (AAS7) or 12 weeks (AAS84).<sup>26</sup> Since ColdU patients may not be exposed to critical temperatures every day, a minimum assessment period of 1 week appears advisable. The ongoing ColdUAS validation study, which includes a 2-week documentation period, will determine the recommended observation period of the ColdUAS.

A main strength of this work is that both within the item generation and selection phase, male and female patients, different age groups (including minors), patients with different disease severity levels, and patients with typical and atypical ColdU were included. In addition, a large proportion of the study population was female, as expected with a higher prevalence of female ColdU patients.<sup>8,28</sup> This ensures that the ColdUAS is suitable for a broad patient population. Furthermore, cognitive debriefing and individual patient interviews, both demonstrating high comprehensibility, as well as an impact analysis were applied during the ColdUAS development to increase its quality and performance, and experienced urticaria experts, who have worked on many PROM projects, have contributed to the development of the ColdUAS.

Limitations of this work include the monocentric design in a mostly Caucasian patient population and the limited number of patients. Thereby, a part of the patients from the item generation phase were included for item selection as well. Additionally, some stages of the item selection process were only performed by female patients. Therefore, it cannot be fully excluded that a larger and more diverse study population from different geographic areas could have resulted in a different outcome. As ColdU is a very rare disease with limitations in recruitment, only a few adolescents ( $n = 3$ ) could be included. Moreover, the development of the ColdUAS was conducted in part during the COVID-19 pandemic. As many individuals changed their lifestyle habits during the pandemic, such as leisure outdoor activities, changes in disease perception may have occurred in ColdU patients.

The ColdUAS will help to determine and monitor disease activity in routine clinical practice and ColdU management including treatment, which is currently difficult.<sup>14,29–31</sup> It will also help with ongoing and future clinical trials in ColdU. Importantly, the ColdUAS will allow for the comparison of disease activity and response to treatment in ColdU subpopulations, that is, patients with typical vs. atypical ColdUAS, patients with and without cryoproteins<sup>32,33</sup> or an underlying clonal mast cell disorder,<sup>34</sup> patients with primary vs. secondary ColdUAS,<sup>3</sup> and patients with acquired vs. familial ColdUAS.<sup>35–37</sup>

In conclusion, the final 4-item ColdUAS is the first PROM for the assessment of disease activity in ColdU patients. With its simple and user-friendly application for adolescents aged 12 years and older, the ColdUAS provides a quick overview of disease activity and status. Furthermore, it can be applied for documentation in daily patient care and clinical trials. Our ongoing validation study of the ColdUAS aims to establish validity, reliability, sensitivity to change, minimal clinically important difference, and the recommended observation period, and a scoring system is being developed.

## CONFLICT OF INTEREST

AG, DA, MB, and TA have no conflicts of interest. SA has received research funds/was advisor for/was speaker for Allakos, ALK, AstraZeneca, CSL Behring, LeoPharma, Moxie, Novartis, Sanofi, Takeda, Thermofisher. MM is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GInnovation, Gilead, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB, and Uriach. KW is or recently was a speaker and/or advisor for and/or has received research funding from Moxie and Novartis. DTM has received research funds/was advisor for Celldex, Moxie, Novartis and Sanofi. JB has received research funds/was consultant and speaker for Novartis, Genentech, Astra Zeneca, Sanofi-Regeneron, Roche and Incyte, and has received research funds/was consultant for Celldex, Amgen, and Allakos.

## AUTHOR CONTRIBUTION

DA and AG performed statistical analysis and drafted the manuscript. DA, TA, and MB were involved in patient recruitment and proofreading of the manuscript. SA, KW, and MM were involved in study planning and proofreading of the manuscript. JB was involved in the translation process and generation of an U.S. American version. DTM has planned the study, coordinated the study, collected patient data, was involved in statistical analysis, and drafted the manuscript.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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