

SPECIAL REPORT

Pruritus Assessment in Clinical Trials: Consensus Recommendations from the International Forum for the Study of Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials

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Chronic pruritus is a common symptom and there is an urgent need to test new anti-pruritic substances in high-quality clinical trials. However, no widely accepted standardized and validated method for objectively measuring pruritus is yet available. A special interest group of the International Forum for the Study of Itch has been established to assess scoring methods and questionnaires for use in clinical trials. This paper presents our current recommendations. The set of measures we recommend includes pruritus intensity scales, instruments for assessment of scratch lesions, chronic pruritus course, quality of life and patient benefits. Key words: itch; pruritus; visual analogue scale; patient benefit index; quality of life; data bank.

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Chronic pruritus (CP) is a worldwide phenomenon, which occurs in every age group and has a high impact on quality of life (QoL). The current estimated prevalence of CP, defined as pruritus lasting for more than 6 weeks, is 16–23% in the general population (1, 2), with a higher prevalence in dermatological patients. Thus, for instance, 100% of atopic dermatitis (AD) and urticaria patients, as well as approximately 80% of psoriasis patients are affected by CP (3). Only a small number of all patients have access to specialized itch clinics and receive specific medical care (1). The majority of patients undergo ineffective therapies. This is partly due to the current lack of licensed anti-pruritic drugs that interfere with the neurobiological mechanisms of the symptom. In addition, some effective topical therapies for this indication are not covered by national insurance. Patients thus have the double burden of inadequate treatment of the symptom and high costs of treatment. CP, as a symptom of a variety of underlying diseases requiring a multi-disciplinary approach, is therefore of high relevance to health economics.

Novel anti-pruritic therapies are urgently needed, especially for certain types of pruritus, such as aquagenic pruritus, prurigo nodularis, atopic dermatitis and cutaneous T-cell lymphoma-related pruritus. In addition to the generation of new hypotheses regarding clinically relevant therapy targets in these disease entities, investigators have to face another challenge. Pruritus is a subjective symptom and cannot be measured objectively. The assessment of the anti-pruritic effect is, to date, based solely on patient reports on the course of itch or measurements of scratch movements (4). The aim of the Special Interest Group (SIG) Scoring Itch in Clinical Trials of the International Forum for the Study of Itch (IFSI; www.itchforum.net) is to define a robust set of valid measures to assess pruritus in clinical studies. We aim to improve the quality of the outcome measures, fulfil the quality criteria of the European Medicines Agency (EMA) and Food and Drug Administration (FDA) regarding patient-reported outcomes, and make it possible to compare results across studies.

To avoid the development of duplicate instruments and to achieve a broad consensus on the choice and employment of available instruments, the SIG was founded in 2009. It comprises a panel of international experts and collaborates with the Japanese Society of Itch and the German working group on pruritus research (some members are the same in both groups) (4–7). Some of the available instruments have already been validated (4, 5) and a questionnaire for the assessment of pruritus in clinical trials has been proposed (8). In this consensus paper, currently available instruments are presented and our first recommendation on a valid set of assessment tools for clinical trials is provided. The SIG will continue to study this subject and will welcome criticism and input during what we expect will be a continuous process of revision and improvement. We are aware of the fact that, for many tools, no validation studies have been performed and versions in other languages are not available yet.

LEGAL REQUIREMENT FOR STUDY DESIGN: INCLUSION OF PATIENT-REPORTED OUTCOMES

It is strongly recommended by nearly all health authorities to include patient-reported outcomes (PRO) into

the study design of randomized controlled trials (RCT). The aim of including PRO is to demonstrate a clinical treatment benefit of the new substance from the patient's perspective (9). PRO are defined as being "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (9). This includes, for example, satisfaction with the therapy, subjective benefit or QoL improvement (9). Thus, PRO comprise single and multi-dimensional measures of symptoms, health-related quality of life (HRQoL), health status, adherence to treatment, and satisfaction with treatment (10). The outcome, as reported by the patients, can be measured in 2 ways: in absolute terms (e.g. intensity scales) or as a change from a previous measure (e.g. comparison of QoL scores) (9). Some single dimensional PRO, such as assessment of change of the core symptom (e.g. by itch intensity scales) may serve as efficacy end-points of the RCT (10). The EMEA has published a reflection paper on regulatory guidance for the use of HRQoL measures in the evaluation of medicinal products (10). According to the EMEA, HRQoL assessment is optional and, because of its multi-dimensionality, cannot serve as the primary end-point. In chronic life-threatening conditions, such as CP, however, HRQoL information may be important for detection of any impact of the symptom on the daily life and social functioning of patients and changes in these parameters during the RCT. Furthermore, such information would enable the attending physician to make a choice between the medicinal products available (10). In this consensus paper, we have taken into account the various health authority requirements and have included several PRO and HRQoL questionnaires into our recommendations.

THE CHALLENGE OF MEASURING ITCH

CP is a symptom of different diseases with correspondingly different underlying mechanisms of cutaneous and extracutaneous pruritus induction. There is, therefore, no uniform clinical profile of itch perception that runs through different patient descriptions of CP. Variations can be observed in terms of localization, duration, quality, intensity, and course of CP. Patients' perception of CP-related impact on QoL, sleep and psychosomatic reactions also differ, though often they demonstrate similar changes. In addition, all these parameters are subjective and vulnerable to confounders, such as current mood, environmental factors or stress. It is therefore important not to rely on only one parameter, such as the intensity of pruritus. Instead, a set of tools addressing different parameters (e.g. quality and course of CP) should accompany the assessment of the intensity. Furthermore, concerning the target indication of the trial, specific characteristics may have to be taken into account (for example scratch lesions or eczema formations) and additional assessment tools must be selected.

Thus, in RCT dealing with new antipruritic substances, selection of the proper pruritus parameters that may serve as PRO, and which reflect the real course of the symptom, is crucial. The current state is now presented here.

INSTRUMENTS FOR DATA COLLECTION ON PATIENT-REPORTED OUTCOMES

Questionnaires

For acquisition of data on CP, several questionnaires have been developed in the past and are currently used; for example, as the Eppendorf Itch Questionnaire (11). No international standardized questionnaire is, as yet, available (11). However, the use of the available questionnaires in the doctor's office is recommended for structured and complete history-taking. In the future, a standard documentation procedure will be developed on behalf of IFSI (11). A questionnaire applicable in RCTs for gathering data on pruritus parameters, which will also allow comparison of parameters during a study, needs to be developed and validated.

Scales for gathering data on pruritus intensity

Gathering data on pruritus intensity is currently the most commonly used PRO in RCTs (4–6). Several scales are available for assessment of pruritus intensity, e.g. multidimensional scales, such as the Itch Severity Scale and the Pruritus Grading System, or monodimensional scales, such as the visual analogue scale (VAS). Multidimensional scales have methodological disadvantages (unequivocal classification is not always possible) and have not been adequately validated in clinical studies. Mono-dimensional scales represent a simple and rapid method for intensity assessment in RCTs and are therefore widely used. Among these, the most frequently employed instrument is the VAS, which was originally used for evaluating pain, but can also be employed for assessing pruritus intensity (4–6). The VAS is a horizontal 10-cm long line, on which patients make a vertical mark to indicate their subjective assessment of pruritus intensity. The end-points are described as follows: 0=no itch and 10=the worst imaginable itch (6). The VAS is usually used as a horizontal line; however, there is also a vertical version of VAS, from which it differs only in small and non-significant ways (5).

The numerical rating scale (NRS) is a similar method of pruritus measurement, with which patients can assess pruritus intensity on a scale of 0 (no pruritus) to 10 (the worst imaginable pruritus). Although the NRS is similar to the VAS, in the validating study it was found that fewer data were missing in the paper-based NRS. In particular, in patients older than 60 years, there was almost double the amount of missing data in the VAS compared with NRS (4). Furthermore, pruritus scores on the NRS were

slightly, although significantly, higher than on the VAS (4). It is still unclear whether these differences have any clinical relevance, for instance in the assessment of therapy effects. Nonetheless, it is advisable to carry out a test, asking patients to complete the VAS form, before it is employed in a clinical study, in order to make study participants acquainted with the instrument and thus minimize the amount of missing data. The verbal rating scale (VRS) is another instrument used in which the severity of pruritus is coded with graduated adjectives (from 0 = no pruritus; to 5 = very severe pruritus).

For a long time, these scales for assessing pruritus remained unvalidated, but this issue has now been addressed in 2 recent studies (4, 5). In a study including patients with itchy dermatoses and patients with chronic pruritus of different aetiologies (a total of 781 European and Japanese patients) it was shown that data from VAS, NRS and VRS showed a high degree of reliability and correlation among each other (4–6). In a test-retest reliability analysis, a high degree of interclass correlation coefficients was found, confirming a good reproducibility of these instruments. Assessment of the areas addressed by VAS was carried out with the help of these studies (Fig. 1).

A short questionnaire for a poll among members of the IFSI was developed, asking the experts for their experience with VAS. Nineteen clinicians and IFSI members of 7 countries participated (Germany, $n=8$; USA, $n=4$; Japan, $n=2$; Poland, $n=2$; France, Turkey and Sweden, each $n=1$). Inclusion of VAS into clinical trials was recommended by 94.7% of participants. The question as to how frequently data should be obtained via VAS in a RCT received varying answers: 75.0% voted for “during study visit and daily via diary”, 18.8% for “only via daily diary”, and 6.2% for “only during study visit”. The target parameters, as follows, were selected: assessment of mean itch (50.0% of participants), worst itch (68.8%), lowest itch (12.5%) and all (6.25%). There was also no consensus on how many times a day the VAS should be scored by patients: once daily (41.2%), twice daily (35.3%), three times daily (23.5%) were the answers. In order to obtain reliable data using the diary method, a preliminary study recommends that patients record their mean or worst pruritus intensity twice daily with the VAS or NRS (12). However, as yet, there are no studies confirming the usefulness of this recommendation. There was a broad consensus that other tools should be included in RCT in order to support the VAS data: quality of life (94.7%), sleep measurement (77.8%), and anxiety/depression assessment (77.8%).

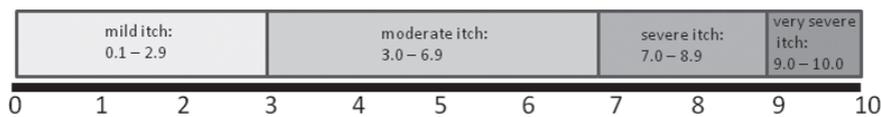


Fig. 1. Areas and severity of pruritus on the visual analogue scale (VAS), as defined according to the study of Reich et al. (5).

Monitoring the course of pruritus

Scores on the monodimensional intensity scales, however, are highly vulnerable to distortion by endogenous and exogenous factors and frequently provide highly subjective data, which is a distinct disadvantage in RCTs. Thus, the VAS may reflect patient satisfaction with the medical care received instead of the true itch intensity, which may lead to false-positive or false-negative results. Beyond that, there are still a great number of questions to be clarified in connection with the optimal use of the pruritus assessment scales (e.g. clinically relevant drop in VAS points, frequency of data collection). Instruments for assessment of pruritus course are still uncommon, but are in the process of being developed. The 5D scale was published in 2008 and claims to serve as a monitoring instrument for the long-term course of pruritus (13). It comprises 5 questions that address the duration (total hours of itch in the past 2 weeks), degree (5-point NRS, see above), direction (change of symptom in the past 2 weeks), disability (QoL items concerning sleep, leisure, etc.), and distribution on the skin areas. There are currently no RCTs that have used the 5D scale. One has to await the results of future studies on the utility and statistical outcome of the 5D scale.

Another new approach is that provided by the novel so-called dynamic pruritus scale (DPS) that indicates current pruritus in relation to the previous state, and thus enables a more precise interpretation of the course of pruritus, something that RCTs in particular require (7). Itch-free days (IFD) is a tool adapted from atopic dermatitis studies, which is currently validated for use in CP patients (7). It measures the total number of days in which there is dramatic improvement of the symptom. The patient global assessment (PGA) summarizes some of the above tools and monitors satisfaction with the treatment from the patient perspective and the overall reduction of CP (7). Preliminary data from studies demonstrated the superiority of the PGA over the VAS.

Patient benefits of anti-pruritic therapy

To directly evaluate patient-relevant benefits on pruritus treatment, the standardized questionnaire “Patient Benefit Index, Version for Patients with Pruritus” (PBI-P) can be employed (8). Prior to treatment, the first page of the PBI-P “Patient Needs Questionnaire” (PNQ) is employed to obtain data on how relevant different benefits of therapy are for the individual patient. After treatment, patients are asked to evaluate the extent to which therapy benefits indicated on the PNQ as relevant to them was in fact realized using the Patient Benefit Questionnaire (PBQ). From all the items taken together, a weighted total benefit

value (the PBI-P in a narrower sense) is calculated, which represents the patient-relevant therapy benefits.

PNQ, as well as PBQ, contain a standardized list of 27 potential variables for capturing data on benefits of therapy, such as being able to sleep better or having to spend less time on daily treatment. These variables for reviewing therapy benefits were developed with the help of interviewing 50 patients with CP. PBI-P has been validated in 100 patients with CP. What the patients wanted most was to have less pruritus, to obtain a clear diagnosis and therapy and to have faith in the therapy. On average, 1.6% of the items were left unanswered. The correlation (convergent validity) between PBI-P and changes in CP measured by the VAS was $r=0.57$; correlation between improved QoL, as measured with the Dermatology Life Quality Index (DLQI) (14), and the PBI-P was $r=0.41$. The PBI-P can be used in clinical practice for gathering data on therapy goals and to evaluate the success of treatment from the point of view of patients. The PBI-P is also suitable for investigating patient-relevant benefits of pruritus therapy in clinical, health economic or healthcare studies.

Supportive scales: quality of life, anxiety, depression and sleep

CP is accompanied by a high level of psychiatric comorbidities (15), and marked sleep disturbances with considerable impact on the quality of life (16). Generic instruments for data gathering on QoL, such as the SF-36 (17) or its shorter version SF-12 (18), are widely used for comparing HRQoL in different diseases. For assessing differences in QoL between different dermatological diseases, the skin-specific instrument the DLQI is widely applied (14). DLQI has also been used to assess QoL in a number of itchy disorders (e.g. psoriasis, prurigo) documenting its usefulness for patients with CP (19). However, for non-dermatological itchy diseases (e.g. cholestatic pruritus) the DLQI may not be appropriate. Despite some disadvantages of DLQI (e.g. DLQI focuses mainly on patient functioning, while mental impairment is assessed to a lesser degree; item bias concerning gender and age, 20), this scale has also numerous advantages, e.g. is available in many languages, has a version adapted for children, and has defined cut-offs for the degree of QoL impairment (14).

ItchyQoL, the first pruritus-specific instrument for data collection on QoL, has recently become available (21). ItchyQoL comprises the 3 dimensions of symptoms, functions and emotions and enables comparison of impairments in QoL of patients with CP, irrespective of the underlying disease. ItchyQoL is currently only available in English and German (21, 22). Future studies and translation into more languages will be of high interest to evaluate the value in studies on CP.

There are a number of instruments that may be used to assess depression and anxiety in dermatological pa-

tients, including those with CP (e.g. Hospital Anxiety and Depression Scale (HADS), Beck's Depression Inventory (BDI), Hamilton Rating Scale for Depression (HDRS)). The HADS (23) is a short, self-assessment questionnaire, and was developed as early as 1983 by Zigmond & Snaith. With the help of the scores of the HADS, the degree of current depression and anxiety level of the patients can easily be estimated. It may serve as a decision tool for inclusion of patients in RCT, as well as a monitoring tool. The BDI (24) is another self-assessment scale originally consisting of 21 questions assessing various aspects of depression. It is recommended that, in patients with somatic diseases (e.g. patients with AD), only the first 13 items concerning cognitive and affective symptoms of depression should be used in order not to overrate the depression level. Scores of >10 points indicate that a patient has depression and may require a psychiatric consultation. The HRSD (25), published for the first time in 1960, was developed to assess the severity of symptoms (mood, agitation, anxiety, sleep deprivation, somatic symptoms) in patients with major depression. Currently, it is one of the most widely used instruments for depression assessment in medical studies. Based on the psychiatric examination, the physician must choose 1 of 3–5 possible answers for each questionnaire item. Scores of <7 points indicates absence of depression, 8–12 suggest mild depression, 13–17 moderate, and >18 points severe depression.

Many patients with CP report problems with falling asleep or waking up frequently during the night. Many of them also regularly use sleep medication (26). It was demonstrated that patients with AD have significant reduction in sleep duration and quality (27). Thus, a measurement of sleeping problems may be a valuable aid in the valid assessment of pruritus. Various instruments have been developed to evaluate sleeping problems and sleepiness. The Stanford Sleepiness Scale (<http://www.stanford.edu/~dement/sss.html>) is a simple tool to assess diurnal sleepiness resulting mainly from insufficient sleep quality. Scores of more than 3 points may indicate significant sleep deficit and the need for more sleep. Another commonly used tool is the Epworth Sleepiness Scale (<http://epworthsleepinessscale.com>). With this questionnaire, patients indicate the probability of falling asleep in different situations using the scoring from 0 to 3. The scale consists of 8 questions. Scores totalling 10 or fewer points is considered as normal, a score of 11–15 may indicate mild to moderate level of daytime sleepiness, while >15 points may result from severe daytime sleepiness or even narcolepsy (28). The intensity of sleep-related problems may also be reliably evaluated with Athens Insomnia Scale, an 8-item questionnaire assessing both sleep quality and diurnal sleepiness (29). None of these scales was rigorously evaluated among patients who have chronic itch (although some studies are ongoing), and it is difficult to recommend which instrument should be chosen for clinical trials. However, based on the analysis

of questionnaire contents, the Athens Insomnia Scale seems to be the most promising one.

Physician assessment: scratching activity

Pruritus induces scratching, which in turn leads to skin changes. Therefore, it would appear that measuring scratch activity or the scratching-associated skin changes is adequate for assessing the symptoms and their course in RCTs. However, as soon as one tries to compare different patients with the same underlying origin of CP, it becomes clear that scratching activity shows inter-individual differences and is influenced by several external factors. Patients with few scratch lesions report that they use different strategies to avoid scratching the skin (self-control by not scratching, wearing gloves, using skin creams/cooling aids instead of scratching). There are different motivations behind this, such as social pressure (typically complaints from the partner regarding scratch activity and its consequences, such as blood stains on bed linen) or avoidance of stigmatization (visible scratch lesions tend to be noticed in professional and social environments). Some patients even report that scratching itself induces pruritus and its worsening; hence they try to avoid scratching. Patients with many scratch lesions may scratch in an automatic fashion and yet others who, as a matter of habit, scratch themselves even in the absence of pruritus. Thus, there is no uniform picture of scratch behaviour and scratching-induced skin changes. Therefore, measuring scratching activity as a parameter of the course of CP is prone to interference and can yield a distorted picture of the

course of the symptom. In RCTs, various instruments for measuring scratching activity have been described (e.g. Accelerometer, Actigraphy, DigiTrac, ActiTrac) (for a review, see 4, 7). There is, as yet, no validation of all these procedures for CP. An instrument for monitoring individual scratch lesions standardized against the body surface, the so-called Scratch Symptom Score (SSS), is currently validated and is probably suitable for measuring reduction in individual scratch lesions (7). A clinical methodological review of pruritus course and scratch behaviour is necessary in order to make a conclusive evaluation of assessment instruments and their value in clinical studies.

RECOMMENDATIONS FOR THE MEASUREMENT OF CHRONIC PRURITUS IN CLINICAL TRIALS

To date, no finally validated set of instruments is available for acquiring data on pruritus in daily clinical routine and for use in studies. However, such instruments are in the process of development within the context of the SIG of the IFSI. The IFSI cooperates over this issue with a German working group (7) and Japanese Itch Society (6). At present, there is consensus among the participating experts that, in clinical trials, the above-presented questionnaires and scales (Table I) can be used for gathering data on PRO in CP. There are still several points that need to be addressed and weaknesses in the tools that need to be eliminated. Future research will provide a basis for revision and refining of our recommendations.

Table I. *Assessment of chronic pruritus (CP) in clinical trials: recommendations for patient-reported outcome (PRO)**

Tool	Recommendation	Reference
Patient-reported outcomes		
Pruritus intensity	Visual analogue scale (VAS) is not an optimal instrument, but currently it cannot be dispensed with. Alternatively, numerical rating scale (NRS) can be used. VAS or NRS should be used in combination with verbal rating scale. Explanation and test run is recommended.	4, 5, 15
Pruritus course	The 5D questionnaire claims to be a tool for assessment of pruritus course; however, due to limited experience, as yet it has not been conclusively evaluated. Three new tools (itch-free days, dynamic pruritus scale, patient global assessment) are currently being validated and will be available in the future. These demonstrated in preliminary studies robust data better than that provided by assessing subjective itch intensity.	14, 16, 17
Patient Benefit Index for pruritus (PBI-P)	PBI-P is an indispensable tool in RCTs. In private practice, for setting therapy goals by doctor and patient together, the PBI-P can be highly valuable.	7
Health-related quality of life (HrQoL)	Data on HRQoL are important as they enable assessment of impact on the daily life and social functioning. The Dermatology Life Quality Index is the instrument most frequently used. The value of the new ItchyQoL has not yet been conclusively evaluated.	18, 28
Anxiety and depression	Acquiring data on anxiety and depression using, for example, the HADS is reasonable both because of the close correlation of the data with the course of CP intensity as also for assessing the need for psychosomatic/psychiatric investigation.	29–32
Sleep	Several instruments to measure sleeplessness in patients are available, e.g. Stanford Sleepiness Scale, Epworth Sleepiness Scale or Athens Insomnia Scale. They may support the data on CP course.	33–37
PRO-independent assessment		
Scratching activity	Devices to capture scratch activity are employed, although methodological studies validating their use in CP are still missing.	Review in 4
Scratching-associated lesions	Currently, data on scratch-related skin lesions can be acquired only in a descriptive fashion. The Scratch Symptom Score is currently under development.	14, 17

*Before employing validated published measuring instruments, it is important to clear up all copyright issues.

Of greatest interest will be the development of tools to assess pruritus in an objective way. Further studies on actigraphy, biomarkers and neuroimaging, including functional magnetic resonance tomography (fMRI), are urgently needed. To date, various fMRI studies have been performed, but have not yet concluded a uniform specific encoding pattern of acute and chronic itch at the neural level (30). Ongoing studies may provide a future tool to evaluate an anti-pruritic response in proof of concept studies.

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