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DISSERTATION

Validation and Critical Evaluation of the Mastocytosis Activity Score

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Preamble

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Abbreviations

AE	= American English
(-)AHN (formerly: -AHNMD)	= (… with) associated hematologic neoplasm (formerly: -AHNMD, - with associated clonal hematologic non-mast cell lineage disease)
ANOVA	= analysis of variance
ASM	= aggressive systemic mastocytosis
BM	= bone marrow
C3a, C5a	= anaphylatoxins (fragments of complement components 3 and 5 respectively, generated during activation of the complement system)
CD	= cluster of differentiation
CM	= cutaneous mastocytosis
DCM	= diffuse cutaneous mastocytosis
Fc region	= fragment crystallizable region
FcγR	= Fc gamma receptor
FcεRI	= high-affinity IgE receptor
FDA	= U. S. Food and Drug Administration
FGF	= fibroblast growth factor
GI	= gastrointestinal
GM-CSF	= granulocyte macrophage colony-stimulating factor
HSCT	= Hematopoietic stem cell transplantation
ICC	= internal correlation coefficient
IFN	= interferon
IgE, IgG	= immunoglobulin E, immunoglobulin G
IL	= interleukin
ISM	= indolent systemic mastocytosis
ISMs+ / ISMs-	= ISM with skin involvement / ISM without skin involvement

KIT	= tyrosine-protein kinase KIT (synonyms: SCFR, stem cell growth factor receptor; CD117, proto-oncogene c-KIT)
MAS	= Mastocytosis Activity Score
MBPs	= major basic proteins
MC	= mast cell
MCL	= mast cell leukemia
MCP-1, MCP-3, MCP-4	= monocyte chemoattractant protein -1, -3, -4 (synonyms: chemokine ligands CCL2, CCL7, CCL13 respectively)
MC-QoL	= Mastocytosis Quality of Life Questionnaire
MCS	= mast cell sarcoma
MCS (of SF-12)	= mental component summary (of SF-12)
MIP	= macrophage inflammatory protein
MIS	= mastocytosis in the skin
MPCM	= maculopapular cutaneous mastocytosis, formerly urticaria pigmentosa
MRGPRX2	= mas-related G-protein coupled receptor X2
MSAF	= Mastocytosis Symptom Assessment Form
M:W	= Ratio of men to women
N	= number of patients
NGF	= nerve growth factor
NSAID	= nonsteroidal anti-inflammatory drug
PCS (of SF-12)	= physical component summary (of SF-12)
PDGF	= platelet-derived growth factor
PGA	= patient global assessment
PRO	= patient-reported outcome
PROMAX	= form of oblique rotation in exploratory factor analysis
PUVA therapy	= psoralen and ultraviolet A light therapy
QoL	= quality of life

RANTES	= regulated on activation, normal T cell expressed and secreted (synonym: chemokine ligand 5; CCL5)
SCF	= stem cell factor
SD	= standard deviation
SF-12	= 12-item Short Form Survey
SF-36	= 36-item Short Form Survey
SM	= systemic mastocytosis
SM-AHN (formerly: SM-AHNMD)	= systemic mastocytosis with associated hematologic neoplasm (formerly: systemic mastocytosis with associated non-mast cell-lineage disease)
SPSS	= IBM SPSS Statistics version 22, IBM Corporation, Armonk, NY, USA
SSM	= smoldering systemic mastocytosis
TGF-β	= transforming growth factor beta
TKD	= tyrosine kinase domain
TKI	= tyrosine kinase inhibitor
TLR	= toll-like receptor
TNF-α	= tumor necrosis factor alpha
UP	= urticaria pigmentosa
VEGF	= vascular endothelial growth factor
WHO	= World Health Organization
Y	= (number of) years

1 Abstract (English)

Background: Mastocytosis is a heterogeneous disease caused by the proliferation of neoplastic mast cells and displays varied clinical presentations. These range from cutaneous symptoms like pruritus or flush to general symptoms of mast cell degranulation like diarrhea, headaches and fatigue. Mastocytosis can also severely reduce a patient's quality of life. The absence of correlating physiological parameters and widely varying individual perceptions of Mastocytosis makes measuring disease activity a challenge. Meanwhile, adequate symptom control is limited and currently no curative treatment for the majority of patients exists. Thus, there is a clear unmet need for new instruments to make disease activity of cutaneous mastocytosis and indolent systemic mastocytosis measurable, thereby allowing for new and improved treatments to be developed.

Objective: The goal of this thesis is to develop a disease-specific disease activity score for cutaneous mastocytosis and indolent systemic mastocytosis, and test its validity and reliability. Current FDA recommendations and a patient-centered model of disease were used in the development of said score.

Methods: Concept elicitation was performed using semi-structured interviews of 10 patients, followed by expert and literature reviews. The resulting 19 potential items were subjected to an exploratory item trial (76 patients) with subsequent testing for face validity and impact analysis. After final item selection, the validity, reliability and potential influencing factors of the final Mastocytosis Acitivity Score (MAS) were tested with a population of 68 patients. A multiple linear regression analysis determined the MAS item-level structure. Finally, MAS was translated from its German original into American English.

Results: The final nine-item MAS demonstrated a three-domain structure: "skin", "gastrointestinal" and "other". The final MAS score showed very good internal consistency reliability and test-retest reliability. Convergent validity and known-groups validity were also confirmed. Age, gender and disease duration did not significantly affect MAS results. A single level item-structure was found to adequately measure disease activity.

Conclusion: The final MAS structure was determined to be a nine item, disease-specific, prospective, single-level instrument. It was found to be a valid and reliable outcome instrument for adult patients with cutaneous mastocytosis or indolent systemic mastocytosis. Following the iterative nature of patient-reported outcome design, MAS is intended to be continually improved as further patient data is accrued. MAS is an important instrument to better measure mastocytosis disease activity, thereby potentially facilitating notable improvements in both routine care and mastocytosis research.

2 Abstract (German)

Hintergrund: Mastozytose beruht auf monoklonal vermehrten Mastzellen. Die Krankheit zeigt eine hohe Variabilität an Symptomen von Pruritus bis hin zu Diarrhö und weiteren Symptomen der Mastzelldegranulation. Mastozytose kann Lebensqualität stark beeinträchtigen. Die Krankheitsaktivität zu messen ist jedoch schwierig mangels spezifisch korrelierender physiologischer Marker und interindividuell variabler Krankheitswahrnehmung. Methoden der Symptomkontrolle sind oft unzureichend. Somit gibt es einen großen Bedarf an Instrumenten, welche die Krankheitsaktivität messen um die Therapie und klinische Forschung von Mastozytose zu unterstützen.

Zielsetzung: Ziel der Arbeit ist die Entwicklung eines Krankheitsaktivitätsscores namens Mastocytosis Activity Score (MAS), der krankheitsspezifisch für kutane und indolent systemische Mastozytose ist und auf Validität und Reliabilität geprüft wird. Die Entwicklung dieses Patient-reported Outcome Instruments soll den aktuellen FDA Empfehlungen folgen, unter anderem durch Nutzung eines patientenzentrierten Krankheitsbildes.

Methodik: Die Itemgenerierung mittels semistrukturierter Interviews von 10 PatientInnen, mit anschließender Expertenkonsultation und systematischer Literaturrecherche ergaben 19 potentielle Items welche durch Befragung von 76 PatientInnen einer Impact-Analyse unterzogen und auf Augenscheinvalidität geprüft wurden. Die Validität, Reliabilität und potentiell den MAS beeinflussende Faktoren wurden anschließend untersucht. Eine multiple lineare Regressionsanalyse bestimmte die Item-Level-Struktur des MAS. Es folgte schließlich die Übersetzung des MAS aus dem Deutschen in eine Amerikanisch-Englische Version.

Ergebnisse: An der finalen Validierungsstudie nahmen 68 Patienten teil. Der finale MAS enthielt neun Items in drei Domänen „Haut“, „Gastrointestinal“ und „Sonstige“. Er zeigte eine gute interne Konsistenz-Reliabilität und Test-Retest Reliabilität. Konvergenzvalidität und Known-Groups-Validität erwiesen sich ebenfalls als vorhanden. Alter, Geschlecht und Krankheitsdauer hatten keinen signifikanten Einfluss auf die MAS Ergebnisse. Eine einstufige Itemstruktur erwies sich als adäquat um die Krankheitsaktivität zu messen.

Fazit: Der finale neun-Item MAS Fragebogen erfasste prospektiv patientenbezogene Endpunkte, war krankheitsspezifisch für kutane Mastozytose und indolente systemische Mastozytose und erwies sich als valide und reliabel. Aufgrund des iterativen Designs des Patient-reported Outcome Scores werden MAS Ergebnisse zukünftig mit mehr vorhandenen Patientendaten weiter auf Validität und Reliabilität geprüft und das Design verbessert. MAS ist ein wichtiges Instrument zur Messung der Krankheitsaktivität von Mastozytose und hat somit großes Potential die klinische Langzeitbetreuung von Mastozytosepatienten sowie die Erforschung der Erkrankung und ihrer Therapie zu fördern.

3 Introduction

3.1 Mastocytosis

Mastocytosis is a heterogeneous group of diseases, all characterized by the proliferation and accumulation of neoplastic mast cells (1). While most cases display cutaneous involvement, mast cell accumulation also occurs in a systemic form with proliferation in bone marrow, lymph nodes and the gastrointestinal tract, along with various other organs (2-4). Due to the varied location of mast cell accumulation, infiltration and activation (both IgE dependent and independent), mastocytosis displays a broad spectrum of symptoms including flush, pruritus, gastrointestinal symptoms, fatigue and bone pain (5). The varied clinical presentation of mastocytosis along with the low prevalence of this rare disease has meant that mastocytosis as a scientific concept has evolved only slowly over time (6, 7).

3.2 History of Mastocytosis

The history of mastocytosis as a clinical concept began in 1869, when Edward Nettleship documented the first case of a 2-year-old girl suffering from multiple wheals (8). Cases were interpreted as chronic urticaria, leaving red-brown lesions on the skin (9). From then on, members of the historic Clinical Society of London discussed and categorized further cases of an independent clinical concept, coined urticaria pigmentosa (UP) by Alfred Sangster in 1878 (10, 11). A year later, Paul Ehrlich became the first to describe and name mast cells, which would become central to the concept of mastocytosis. In 1887 Paul Unna discovered mast cell proliferation in skin biopsies of UP patients (12, 13). Meanwhile, Ferdinand-Jean Darier advanced the clinical understanding of the disease by demonstrating that rubbing patients' skin lesions consistently elicits urtication, an important sign of cutaneous mastocytosis, later named Darier`s sign after it's discoverer (11). In 1936, A. Sezary coined the term mastocytosis, however up until the middle of the 20th century, the concept pertained solely to skin lesions (14, 15). In 1949, John M. Ellis first described a systemic form of mastocytosis after he found mast cell conglomerations in multiple organ tissues in an autopsy case (16). From the late 1960s onwards, the signaling pathways involved in mast cell differentiation and activation

have been described in ever greater detail, while the clinical and epidemiological characteristics of the disease have been found to be ever more intricate (11). In an attempt to incorporate all relevant new subgroups of mastocytosis into one classification system, WHO Criteria and Classification of Mastocystosis were published in 2001 for the first time (17). In 2016, the latest update of the WHO Criteria was released, taking into account discoveries of biomarkers and targeted therapies, thereby refining diagnostic categories and improving their prognostic relevance (18). Meanwhile, an in-depth understanding of mast cells remains the cornerstone of current mastocytosis research.

3.3 Mast Cells

Human mast cells develop from CD34+ hematopoietic, pluripotent stem cells of the bone marrow (19, 20). These cells differentiate further and migrate into vascularized tissue as CD34+/CD117+ mononuclear agranular progenitor cells (1, 21). In peripheral tissues progenitors fully mature to become mast cells, each with tissue-specific phenotypes influenced by their respective microenvironment (22). Although found in all vascularized tissue, the most common microenvironment for mast cell maturation are the interfaces between host tissue and the external environment, such as the respiratory tract, gut mucosa, as well as the skin (23, 24).

During most of mast cell research the mast cell was seen mainly as an effector of allergic reactions, particularly of the kind mediated by IgE. Such reactions occur when a multivalent antigen cross-links an antigen-specific IgE, bound to a high-affinity IgE receptor (FcεRI) on the mast cell surface (25). FcεRI aggregation subsequently promotes the degranulation of mast cell mediators causing symptoms associated with allergy such as flush and mucus secretion (26). IgE-mediated allergic reactions however, are only one facet of mast cell function with these cells also acting as important sentinels of the immune system and responding both directly and indirectly as effector cells toward pathogens (27). Along with their role in adaptive and innate immunity, mast cells are known to be involved in immune tolerance, angiogenesis, wound healing and tissue repair depending on their respective microenvironment (25).

The enormous variety of mast cell microenvironments is reflected in the manifold triggers of mast cell activation. Table 1 illustrates this wide array of triggers of degranulation. The effects of such triggers differ according to the mast cells'

microenvironment and stage of maturation (28). The anaphylatoxin C5a for instance, induces the chemotaxis of mast cells, but also causes degranulation specifically of cardiac mast cells (29). Along with the well-researched activation mechanism via IgE during type I hypersensitivity reactions, IgE independent activation such as via IgG, chemokines and various other cytokines is also prevalent (30). Meanwhile, the mas-related G-protein coupled receptor X2 (MRGPRX2) is involved in pseudo-allergic reactions (31). Toll-like receptors (TLRs) on the other hand recognize molecular patterns from bacteria, viruses, parasites, as well as patterns related to tissue damage (32).

Table 1: Common stimuli and receptors of mast cell activation

Common stimuli and receptors of mast cell activation – as adapted from Caslin et al. (28)	
Stimuli	Corresponding MC receptor
IgE	FcεRI
IgG	FcγR
Anaphylatoxins C3a and C5a	Complement receptors
Pathogen-associated molecular patterns	Toll-like receptors
Compound 48/80, neuropeptide substance P	MRGPRX2
Chemokines	Chemokine receptors including CCR1, CCR3-5, and CXCR1-4
Cytokines including IL-3, IL-4, IL-33	IL-3R, IL-4R, IL-33R

Abbreviations: Ig, immunoglobulin; CD, cluster of differentiation; IL, interleukin; MRGPRX2, mas-related G-protein coupled receptor X2

Activation of mast cells leads to degranulation by way of exocytosis (33). Table 2 displays some of the common mast cell mediators, including histamine, proteases and proteoglycans such as heparin (34, 35). During degranulation, preformed mediators like histamine and tryptase are released during the first 5 to 30 minutes (36). Phospholipid metabolites like prostaglandins, leukotrienes and platelet-activating factor are newly formed before release. Two to six hours after activation, mast cells finally synthesize (neosynthesis) chemokines and cytokines (like IFN) due to altered gene expression (30, 36, 37). While some mast cell mediator release is modulated such as histamine release modulated by IgE, other mediators like tryptase are released at constant rates (18). Thereby, serum tryptase levels can be utilized as a measure of mast cell load, a measure both of diagnostic and therapeutic significance for example in IgE antibody therapy with omalizumab (18, 38). Along with increased mast cell activation and degranulation, increased mast cell load is one of the defining characteristics of mastocytosis.

Table 2: Examples of mast cell mediators - as adapted from da Silva et al. (25)

Examples of mast cell mediators – as adapted from da Silva et al. 2014 (25)	
Preformed mediators	
Biogenic amines	Histamine, serotonin, dopamine, polyamines
Lysosomal enzymes	Beta-hexosaminidase, beta-glucuronidase, beta-D-galactosidase, arylsulphatase A, cethepsins C, B, L, D, and E
Proteases	Chymase, tryptase, carboxypeptidase A, cathepsin G, granzyme B, matrix metalloproteinases and renin
Other enzymes	Kinogenases, heparanase, angiogenin and active caspase-3
Proteoglycans	Serglycin (heparin and chondroitin sulphate)
Cytokines	TNF-alpha, IL-4, IL-5
Chemokines	RANTES (CCL5), eotaxin (CCL11), IL-8 (CXCL8), MCP-I (CCL2), MCP-3 (CCL7), MCP-4
Growth factors	TGF-beta, bFGF-2, VEGF, NGF, SCF
Peptides	Corticotropin-releasing hormone, endorphin, endothelin-I, LL-37/Cathelicidin, substance P, vasoactive intestinal peptide
Others	Eosinophil Major Basis Protein (MBP)
Neoformed mediators	
Phospholipid metabolites	Prostaglandin D2 and E2, leukotrienes B4, C4 and platelet activating factor
Neosynthesized mediators	
Cytokines	IL-33, IL-10, IL-12, IL-17, IL-5, IL-13, IL-1, IL-2, IL-3, IL-4, IL-6, IL-8, IL-9, IL-16, type I and type II IFN, MIP-2beta
Growth factors	SCF, GM-CSF, beta-FGF, NGF, PDGF, TGF-beta, VEGF
Reactive oxygen species	Nitric oxide
Others	Complement factor C3 and C5

Abbreviations: FGF, fibroblast growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor, IL, interleukin; MCP, monocyte chemotactic protein; NGF, nerve growth factor; PDGF, platelet-derived growth factor; RANTES, regulated upon activation, normal T cell expressed and secreted; SCF, stem cell factor; TGF-beta, transforming growth factor-beta; IFN, interferon; TNF-alpha, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; MIP-2beta, macrophage inflammatory protein-2 beta.

3.4 Pathogenesis of Mastocytosis

All forms of mastocytosis display an accumulation of clonal neoplastic mast cells (4, 24). Mast cells are involved in inflammatory reactions via a unique composition of mediators and antigens (20, 25, 39). Committed mast cell progenitors express the tyrosine-protein kinase KIT (CD117), a receptor which binds stem cell factor (SCF) (25). CD117 dimerization and subsequent activation by SCF is important for the maturation, survival and functioning of mast cells (21). Although progenitors of many CD34 positive stem cell lines express KIT, with pleiotropic effects, only mature mast cells (and melanocytes) retain this receptor as cellular differentiation progresses (20, 25, 40). In humans, KIT is encoded on chromosome 4q12, in a 21-exon gene (41). The receptor is comprised of four domains; an extracellular, transmembrane, juxtamembrane and tyrosine kinase domain (41-44). It is the tyrosine kinase domain (TKD), specifically the subsection phosphotransferase domain, which is subject to frequent structural altercations due to KIT gene mutations (40). The most common of the over 20 known KIT gene mutations in systemic mastocytosis (SM) is the substitution of valine for aspartic acid in exon 17, called D816V (40). In cohort studies, 80-90% of patients with SM exhibited KIT D816V receptors on neoplastic mast cells (45, 46). Although pediatric cutaneous mastocytosis (CM) displays a comparatively greater variety of KIT mutations, including mutations of exons 8 and 9, the most common mutation remains KIT D816V affecting 30% of cases (45, 47, 48). KIT D816V mutations cause a change in the receptor's catalytic site, thereby allowing constitutive ligand-independent activation (44, 48). Auto-activation of KIT D816V thus acts as a constant driver of maturation and differentiation in neoplastic mast cells and their progenitors (49, 50). This is however not the sole trigger of neoplastic transformation, evidenced by the fact that both indolent systemic mastocytosis (ISM) and smoldering systemic mastocytosis (SSM) can show high levels of KIT D816V without high rates of progression (51, 52).

KIT D816V gained clinical significance not only due to its large prevalence in systemic mastocytosis and cutaneous mastocytosis, but also because of the correlations between the KIT D816V allele burden, mast cell load, patients' survival rate and prognosis (53, 54). KIT D816V allele burden also affects treatment efficacy as the persistently active protein conformation prevents the binding of and so confers resistance toward some tyrosine kinase inhibitors (TKI) like imatinib (40). For this reason, while some non-targeted cytoreductive treatments like Interferon alpha or cladribine can be used, targeted

therapies against KIT such as the newer TIKI midostaurin are gaining ever greater importance in therapy regimens (55). Proteins further downstream in the KIT signaling pathway have also been identified as potential sites for targeted therapy, albeit to date have not shown a relevant therapeutic effect (18). Thus, KIT D816V remains one of the most important factors in the pathogenesis and treatment of this rare disease.

3.5 Epidemiology of Mastocytosis

Mastocytosis is a relatively rare illness and few studies have been conducted on the epidemiology of the disease. According to a study of Danish national health records, the incidence rate of all mastocytosis subtypes in adults from 1997-2010 in Denmark was 0.89 per 100,000 per year with a cumulative incidence among adults of 12.46 per 100,000 over that time period (6). In Denmark the total prevalence on the 1st of January 2011 was 9.59 per 100,000 (6). A study in the Groningen region of the Netherlands in 2013 showed a similar prevalence of 13 per 100,000 (56). However, these figures do not take into account probable large numbers of undiagnosed cases (24). Particularly systemic forms of mastocytosis are prone to being under-diagnosed due to the wide range of symptoms that can be presented, along with frequent overlaps with further illnesses (57). Furthermore, both the treating physician and the analyzing pathologist require expertise, especially in recognizing and identifying this rare illness, thereby potentially complicating the diagnosis (6). Study results are inconclusive as to the gender distribution among mastocytosis cases with some authors citing a ratio of 1.5:1 (m:w) while others citing no difference in distribution between the sexes (38, 58-60). Mastocytosis (of all types) disproportionately affects children with 2/3 of patients aged under 18 (48). Over 80% of pediatric patients suffer from cutaneous mastocytosis (61). Thus, cutaneous mastocytosis is the most common form of the disease overall. The most common form of mastocytosis among adults is indolent systemic mastocytosis (62). With the disease displaying a wide range of clinical symptoms the WHO Criteria and Classification of Mastocytosis is ever more important.

3.6 Classification of Mastocytosis

The WHO Criteria and Classification of Mastocytosis differentiates types of mastocytosis by clinical and histological criteria with each group having a different prognosis (17, 63). It divides the disease into two broad categories; cutaneous mastocytosis (CM) and systemic mastocytosis (SM) (11). CM involves neoplastic mast cell accumulation solely in the skin, whereas SM displays at least one instance of non-cutaneous mast cell infiltration (18). SM however often also involves the skin with over 80% of patients suffering from skin lesions (64). CM is most commonly found in children and has a good prognosis with remission being common during adolescence (17). Although CM usually manifests at a young age, adult onset can occur (65). As seen in Table 3, CM can be divided into mastocytoma of the skin (or solitary mastocytomas), maculopapular cutaneous mastocytosis (formerly urticaria pigmentosa, UP) and diffuse cutaneous mastocytosis (66). Unlike CM, SM is most likely to manifest between the ages of 20 to 40. SM has a varied prognosis ranging from normal or near-normal, to a greatly reduced life-expectancy (17). The 2016 update to the WHO classification caused a reclassification of mastocytosis cases and divides SM into indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with associated hematologic non–mast cell-lineage disease (SM-AHN), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), as well as the separate group of mast cell sarcomas (MCS) (18, 67).

Table 3: WHO Classification of Mastocytosis (18, 68, 69)

WHO Classification of Mastocytosis 2016 (18, 68, 69)
Cutaneous mastocytosis (CM) - Maculopapular CM (MPCM) (formerly urticaria pigmentosa) - Mastocytoma of the skin (cutaneous solitary mastocytoma) - Diffuse CM (DCM)
Systemic mastocytosis (SM) - Indolent SM (ISM) - Smoldering SM (SSM) - SM with associated hematologic neoplasms (SM-AHN; formerly: SM-AHNMD) - Aggressive SM (ASM) - Mast cell leukemia (MCL)
Mast cell sarcoma (MCS)

Abbreviations: SM-AHNMD, systemic mastocytosis associated with clonal hematologic, non-mast-cell lineage disease

3.6.1 Cutaneous Mastocytosis

The most common form of CM is maculopapular CM (MPCM) constituting around 2/3 of CM cases (66). As in all forms of CM, MPCM involves the accumulation of neoplastic mast cells in the dermis. MPCM replaced the term urticaria pigmentosa (UP) and aims to highlight that this subgroup involves stable lesions of mast cell accumulation rather than transient urtication as the name urticaria pigmentosa suggests (70). MPCM mainly affects children with most cases being diagnosed at under two years of age (60). In adults, MPCM is rare and can only be diagnosed if SM is ruled out by bone marrow biopsies (38). Patients typically display red to light brown macula on the trunk (60, 66). According to the size and shape of lesions, MPCM or UP can be divided into monomorphic UP and polymorphic UP (71). These macula can also spread centripetally and symmetrically, usually sparing palms, face and scalp (66, 70). Depending on the degree of mast cell proliferation or burden, these macula can range in appearance and size from a few millimeters to centimeters (38). The mast cell burden also determines the likeliness of symptoms related to mast cell degranulation due to physical stimuli like hot baths or exercise (72). Such symptoms include pruritus, urtication and flush (57). The Darier's sign is however visible in almost all MPCM cases and is therefore used in clinical diagnosis (38). Mast cell accumulation occurs mainly in the papillary and reticular dermis thereby increasing the risk of atopic diseases (73). Familial recurrences of MPCM have been cited, but remain the exception (38). The prognosis of MPCM is good with most patients experiencing a regression of symptoms during puberty and around 50% a complete remittance during this age (60).

Solitary mastocytomas, or mastocytoma of the skin, can occur during all stages of life, but commonly manifest at birth or during the first three months of infancy (45). Patients exhibit nodules or elevated plaques which are sharply demarcated and yellow to red-brown in color (69). Such lesions can range from four to five centimeters in diameter and can affect the entire integument, most commonly involving the extremities while sparing palms of hands and soles of feet (74, 75). Additionally, it is also possible for patients to exhibit bullae in the area of the lesion (48). It is rare for patients to exhibit more than one mastocytoma of the skin and cases with more than three lesions are considered to be MPCM (48). As in all cutaneous forms of mastocytosis, pruritus occurs in roughly 50% of cases (48). Darier's sign is often positive along with possible flushing, however systemic symptoms of mast cell degranulation are rare due to the low mast cell burden

in this mastocytosis form (48, 66). Similar to MPCM, most cases of mastocytoma of the skin undergo full remission during adolescence (45).

Diffuse erythrodermic cutaneous mastocytosis or diffuse cutaneous mastocytosis (DCM) is rare, making up <1% of CM-cases, however it represents the most severe form of CM (71). Patients are usually asymptomatic at birth and develop lesions within the first three months of infancy (45). DCM lesions display a thickening of the dermis similar to peau d'orange (76). They involve generalized red to brownish erythematous papules often with bullae or blistering of affected skin (48). Similar to MPCM, dermographism is common among DCM cases (48). Patients also have a high mast cell load often causing severe symptoms of mast cell degranulation, like diarrhea, hypotonia and distributive shock (66). Serum tryptase can thus be elevated even without extracutaneous mast cell accumulation (48). In particular, DCM cases of familial mastocytosis with germ-line c-kit mutations involve an elevated risk of chronic disease and disease progression to SM-forms (48). Compared with other forms of CM, cases of DCM are considered to have a more guarded prognosis (77).

3.6.2 Systemic Mastocytosis

Systemic mastocytosis (SM) is defined as an accumulation of neoplastic mast cells in at least one extracutaneous tissue (18). Unlike CM, which is more prevalent in children, SM predominantly affects adults (7). According to the WHO diagnostic criteria for SM, SM patients must fulfill either one major WHO criterion and at least one minor criterion, or alternatively at least three minor criteria (78). As seen in Table 4, the major criterion for SM is defined as multifocal infiltrates of mast cells (with ≥15 mast cells in aggregates) in bone marrow and/or other extracutaneous organs (24). While mast cell accumulation is also seen in tissue other than bone marrow (BM), such as gastrointestinal, hepatic, splenic or osteolytic infiltrates, only BM biopsies are commonly used in diagnosing the disease (79). Minor criteria of SM involve >25% of mast cells in infiltrates being spindle-shaped or having an atypical morphology, or >25% of mast cells in bone marrow aspirate smears being immature or atypical (18). The detection of an activating point mutation of codon 816 of KIT in blood, bone marrow and/or other extracutaneous tissue; and mast cells expressing CD2 and/or CD25 are further minor criteria of SM (18). Finally, serum tryptase levels persistently exceeding 20ng/mL concludes the four minor criteria of SM

(78). It must be noted that serum tryptase levels cannot be taken into account if the patient has an associate clonal myeloid disorder (18).

As seen in Table 3, SM is divided into indolent SM, smoldering SM, SM with associated non-mast cell hematologic neoplasm (SM-AHN), aggressive SM (ASM) and mast cell leukemia (MCL) (4). The groups differ in the degree of mast cell burden, subsequent organ dysfunction, rate of progression and prognosis (80). There are clinical, laboratory and histologic criteria used to differentiate between the various groups (18). Along with major and minor criteria, Table 4 describes B- and C-findings that play a role in differentiating the different subtypes of SM. B-findings are signs of organ involvement such as organomegaly (including lymphadenopathy, splenomegaly and hepatomegaly) with normal organ function, dysmyelopoiesis like hypercellular marrow or discrete signs of myelodysplasia (79). A mast cell burden of >30% infiltration grade in bone marrow and serum tryptase levels of >200ng/mL also constitute B-findings (4). C-findings on the other hand are signs of impaired organ function (57). These can include amongst others, reduced liver function with hepatomegaly, ascites and/or portal hypertension, cytopenia without non-mast cell hematopoietic malignancy, pathologic bone fractures due to osteolysis, weight loss due to malabsorption, as well as splenomegaly with hypersplenism (18). In the following, the various types of SM will be discussed in greater detail.

Table 4: Diagnostic criteria for systemic mastocytosis (69)

Criteria for systemic mastocytosis including B-findings and C-findings	
The diagnosis of systemic mastocytosis requires 1) one major criterion and at least one minor criterion or 2) three minor criteria	
Major criteria	- Multifocal dense aggregates of 15 or more mast cells in bone marrow and/or one or more other extracutaneous organs, confirmed by tryptase immunohistochemistry or other special stains
Minor criteria	- >25% of mast cells in the infiltrate in extracutaneous organs or in the blood exhibit atypical or spindle-shaped morphology - Evidence of a KIT mutation in codon 816 in bone marrow or another extracutaneous tissue - Co-expression of CD2 and/or CD25 on mast cells in bone marrow, blood or another extracutaneous organ - Persistently elevated baseline serum tryptase levels >20ng/mL (except in cases with additional clonal myeloid disease)
B- and C-findings help differentiate SM-subgroups	
B-findings	- Bone marrow biopsy with ≥30% mast cell infiltration (focal, dense aggregates) and elevated tryptase levels ≥200ng/mL - Signs of dysplasia or myeloproliferation in non-MC lineages without a definitive diagnosis of a hematopoietic neoplasm, with normal/slightly abnormal blood count, or hypercellular bone marrow - Hepatomegaly without impaired liver function and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging
C-findings	- Bone marrow dysfunction with one or more cytopenia(s) - Palpable hepatomegaly with impaired liver function, ascites and/or portal hypertension - Skeletal involvement with large osteolytic lesions and/or pathological fractures - Palpable splenomegaly with hypersplenism - Malabsorption with weight loss due to gastrointestinal mast cell infiltrates - Further life-threatening organ damage due to mast cell infiltration

Abbreviation: MC, mast cell

Indolent systemic mastocytosis (ISM) is the most common type of SM constituting around 90% of all SM (62). ISM is however likely to be under-diagnosed since even though most adult cases of CM involve a systemic component, not all patients with skin manifestations undergo bone marrow biopsies (6, 81). The disease meets the criteria for SM, albeit does not have C-findings and thus shows no organ dysfunction due to a high mast cell burden (82). Skin involvement is common in ISM patients, with around 66-75% of ISM patients displaying MPCM-like skin lesions while also suffering from symptoms of mast cell degranulation (17, 83). Since patients with ISM commonly have a normal life expectancy, therapy is mainly symptomatic with a focus on avoiding possible triggers of degranulation (82, 84). The rate of progression of ISM to a more aggressive form is relatively low at around 5% to 10% of patients with good independent prognostic indicators for progression-free survival being serum beta2-microglobulin levels and KIT D816V variant allele frequencies (84).

Smoldering systemic mastocytosis (SSM) is rare compared to ISM (85). In addition to the diagnosis criteria of ISM, SSM shows at least two B-findings (57). Although the mast cell burden is very high in SSM, C-findings are not present (51, 86). Thus, patients with SSM do not have organ dysfunction due to their illness. SSM has a higher rate of progression and a less favorable prognosis compared with ISM (18, 87).

Aggressive SM (ASM) is a rare subtype involving decreased organ function due to mast cell infiltration (4). This mastocytosis subtype is defined as having one or more positive C-findings (with no evidence of mast cell leukemia) in addition to fulfilling the general criteria of SM (18). The actual burden of disease resulting from such infiltration can vary greatly (80). ASM involves changes in bone marrow architecture due to mast cell infiltration (18). In bone marrow smears less than 20% of cells are neoplastic mast cells while no mast cells should be found in peripheral blood smears (4). It is uncommon to find skin lesions in ASM (88). An important distinction to SM-AHN is the absence of other hematologic diseases (18).

Systemic mastocytosis with associated non-mast cell hematologic neoplasm (SM-AHN) is a subtype of SM which entails all cases satisfying both diagnostic criteria for SM as well as criteria for a non-mast cell hematologic neoplasm (88). SM-AHN constitutes around 5% to 20% of all SM cases (4). SM cases without skin involvement are particularly at risk of progressing to SM-AHN or mast cell leukemia (MCL) (4). In SM-AHN cases myelodysplastic syndromes are more common than lymphoid neoplasms (18). It can however be difficult to distinguish between SM-AHN and MCL (18).

Mast cell leukemia (MCL) is the most aggressive form of SM. This rare subtype of SM makes up less than 1% of all mastocytosis cases and is found almost entirely among adult patients (89). It is defined as SM with neoplastic mast cells constituting ≥20% of cells in bone marrow smears being neoplastic mast cells or ≥10% in blood samples (18). A subtype of MCL is the aleukemic MCL in which the proportion of circulating mast cells in blood samples is under 10%, thus making cytolytic analysis of both bone marrow and blood samples necessary for a complete diagnostic workup (4, 89). A transformation from aleukemic MCL into classic or overt MCL is also possible (90). In addition, a distinction is made between primary MCL which develops de novo, and secondary MCL as a progression of existing mastocytosis (usually from ASM or MC sarcoma) (91). MCL is a severe subtype of SM with a high burden of disease (4). Although mast cell burden is high and symptoms of mast cell degranulation occur early in the course of the disease, skin lesions are not present in this subtype of SM (88). Progressive C-findings later follow with multi-organ failure manifesting within weeks to months after diagnosis (91). A severe coagulation disorder often causes bleeding in the gastrointestinal tract among other organs and with no curative therapy available survival times are often no longer than one year (4).

The mast cell sarcoma (MCS) constitutes the final subgroup of mastocytosis in the WHO Classification. MCS is an aggressive yet rare subgroup (1, 18) with solitary accumulations of immature mast cells displaying sarcoma-like destructive growth into surrounding tissue (4). Systemic involvement in the form of SM is not present in this subtype, however MCS can quickly transform into MCL (92). The prognosis of this rare subtype is poor and with no curative therapy available, median survival at diagnosis has been reported as 12 months (92).

3.7 Symptoms of Mastocytosis

Owing to mast cells being located in a wide variety of tissues and releasing a diverse array of mediators during degranulation, symptoms of mastocytosis can be difficult to associate with the disease (57). In particular, subtypes of SM without cutaneous involvement make diagnosis challenging (93). For this reason, it is important to consider mastocytosis as a possible differential diagnosis when confronted with inexplicable signs of mast cell degranulation (79).

Symptoms of systemic mastocytosis originate either from the actual accumulation of mast cells with possible organ dysfunction or from the degranulation of mast cells (75). Upon mast cell activation cutaneous signs of mastocytosis include flushing, pruritus and localized edema (79). Mast cell degranulation can also cause gastrointestinal symptoms such as nausea, diarrhea, vomiting or abdominal cramps. Mast cell mediator release can also affect the cardiovascular system with symptoms such as hypotonia, tachycardia, palpitations, dizziness or syncope (78). Along with the impact of such symptoms on quality of life and mental wellbeing in general, mast cell degranulation may cause or trigger further neurologic and psychiatric conditions such as depression, sleep disturbance and headaches (94, 95). Constitutional symptoms such as fatigue, arthralgia, myalgia, sweats and chills can also occur. In addition to anaphylaxis, skeletal involvement of SM in the form of osteoporosis and pathologic bone fractures is also common (96). Due to the varied and non-specific nature of mastocytosis symptoms, every diagnostic workup should rule out all other causes of organopathy (79). Importantly, not only is there a wide spectrum of mastocytosis symptoms, but also a wide array of how these symptoms are perceived and how they affect a patient's wellbeing (79).

3.8 Diagnosis of Mastocytosis

The diagnosis of mastocytosis involves the evaluation of mast cell related symptoms and possible associated triggers (80). As shown in Figure 1, clinical suspicion is raised with signs and symptoms of mast cell degranulation and/or otherwise unexplainable organopathy (97). Following this, serum tryptase levels must be measured (79). SM usually exhibits high serum tryptase levels of >20ng/ml and a study has demonstrated a correlation between such elevated values and a high mast cell burden (57). Only after both symptoms and the serum tryptase level results coincide with possible SM should biopsies be used to confirm the diagnosis (57).

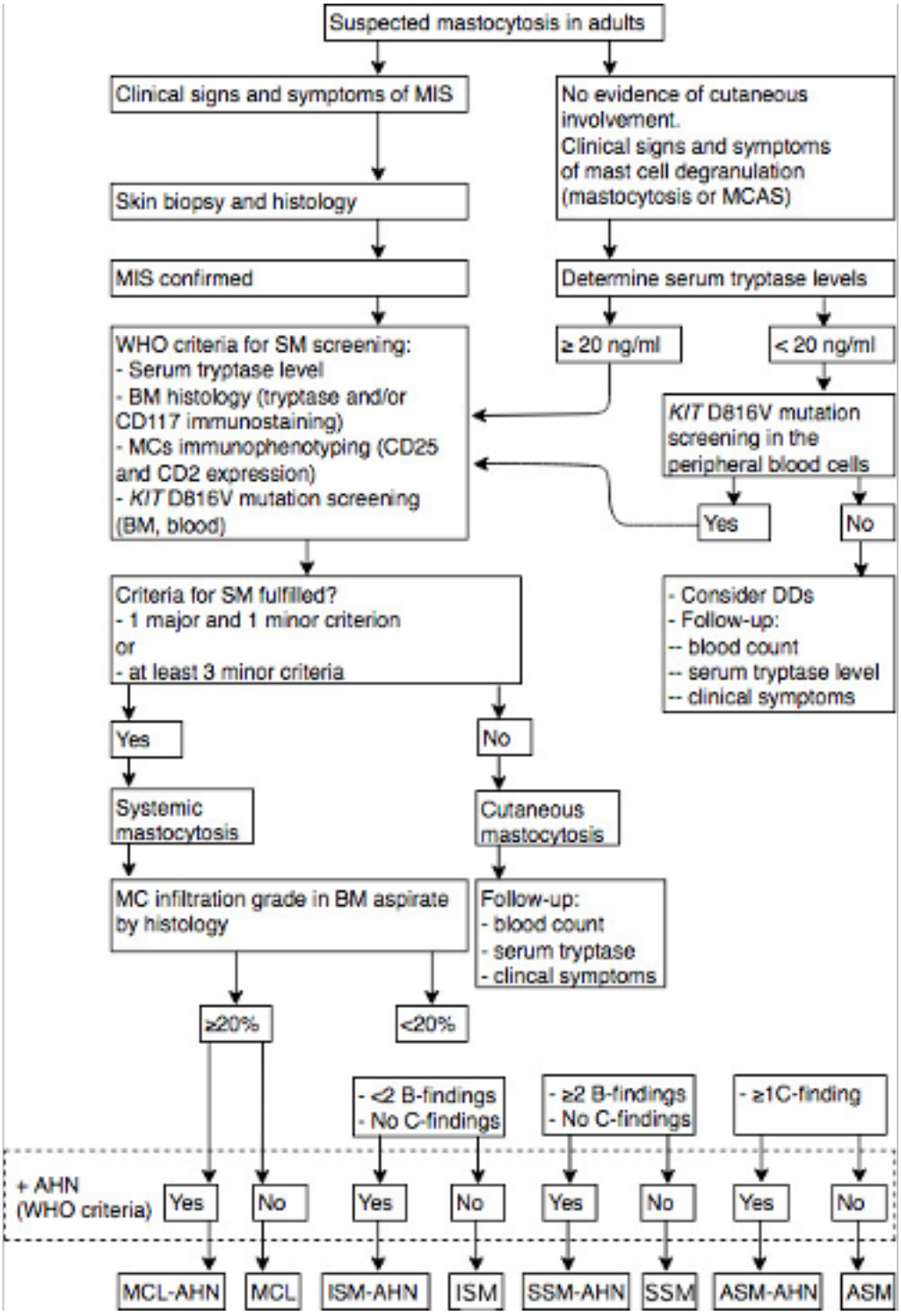
The decision for a diagnostic workup of mastocytosis with cutaneous involvement is also based mainly on clinical grounds including skin manifestations, Darier's sign and/or signs of systemic mast cell degranulation (97). Further investigations involve a skin biopsy of the affected area before confirming mastocytosis in the skin (MIS) (97). MIS is not a separate subgroup of CM or SM in its own, but rather an initial diagnosis requiring further investigation before the case can be categorized as CM or SM (98). MIS does not rule

out further systemic involvement and includes all mastocytosis patients with skin involvement who have not undergone a bone marrow biopsy (99).

If a patient exhibits clinical signs of systemic mast cell degranulation without skin involvement, the highest of three serum tryptase measurements is taken as guide for further diagnostics (97). Serum tryptase levels over 20ng/mL suggest unusually high mast cell activity and thus requires further diagnostic workup to exclude SM (79). Serum tryptase levels below 20ng/mL make abnormal mast cell activation less likely, however do not exclude the presence of neoplastic mast cells involved in mastocytosis (79). To distinguish regular mast cells from neoplastic ones, peripheral blood cells are screened for a KIT D816V mutation (54). If the screening is positive, further diagnostic workup to exclude SM is recommended. If no KIT D816V mutations can be detected, further workup to rule out differential diagnoses should be considered.

Screening for SM follows the WHO Classification of Mastocytosis (68). As described in Table 4, a diagnosis of SM involves the fulfilling of either the major criterion of ≥15 mast cells in aggregates detected in bone marrow biopsies (and/or other extra-cutaneous organs) and a minor criterion, or the fulfilling of at least three minor criteria (18). B- and C-findings are finally used for the definitive differentiation between the SM subtypes (79).

Figure 1: Overview of diagnostic steps for adults with mastocytosis (79, 97)



Basic overview of diagnostic steps of diagnosing mastocytosis in adults. This algorithm is based on data published by Lange et al 2016 (97), and Pardanani et al 2016 (79).

Abbreviations: MIS, mastocytosis in the skin; MCAS, mast cell activation syndrome; SM, systemic mastocytosis; BM, bone marrow; MCs, mast cells; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; DD, differential diagnosis; B and C findings, see Table 4.

3.9 Therapy of Mastocytosis

Mastocytosis therapy is as varied as the disease itself and is always optimized on a case by case basis (38, 100). Thus, although treatment of mastocytosis has undergone considerable changes in recent years, there is still no established guideline for treatment (38). For patients with mild forms of mastocytosis (CM, ISM and SSM), C-findings are not present and most cases show a good prognosis (46, 82). The main focus of therapy for such patients is improving quality of life through the reduction and prevention of mast cell degranulation rather than the reduction of mast cell burden (17). The first measure to reduce symptoms of mast cell degranulation is to identify possible triggers (73). Once triggers including emotional stress, physical stimuli (e.g. hot baths), medication (e.g. acetylsalicylic acid), alcohol and allergic triggers (e.g. bee stings) are known, they can be actively avoided (100). Nonetheless, symptoms can occur regardless of triggers and patients with a cumulative prevalence of anaphylaxis in mastocytosis patients between 22% and 49% in adults (101, 102). For patients with clonal SM or with a history of anaphylactic shock, epinephrine pens should be provided to treat severe forms of mast cell degranulation (100).

Continued monitoring of patients is the second mainstay in treatment of mild forms of mastocytosis (79). By regularly reassessing a patient's symptoms and looking for new B- or C-findings a treatment's effectiveness and possible disease progression can be monitored (57). Several novel approaches of predicting disease progression are currently under development with the hope of further improving disease management (103, 104). In 2014, Hoermann et al demonstrated KIT D816V mutation allele burden could predict a response to treatment and survival (105).

The reduction of existing symptoms also provides major improvements to quality of life. For CM and cutaneous manifestations of SM, especially DCM and mastocytoma, treatment begins with topical steroids (38, 57). Oral steroids can also be used in escalated therapy to reduce blistering and bullous cutaneous lesions, but are not suited for long-term therapy (57). Phototherapy in the form of UV-A, UV-B or psoralen plus UV-A (PUVA) is also effective in the treatment of cutaneous manifestations of mastocytosis (106, 107). It reduces dermographism and skin thickness in DCM and is very effective in reducing pruritus (38, 108). However, the clinical effects only last for a short-term period in most patients, which stresses the risk-benefit-ratio (109). Thus, UV-irradiation should only be applied to exceptional cases and special care needs to be given in children (109).

Extracutaneous symptoms of SM require different and more systemic approaches to treatment. Histamine antagonists are used both in the treatment of skin lesions (H1 antagonists) and symptoms of the gastrointestinal (GI) tract (H2 antagonists) (18, 110). H1 antagonists are particularly useful for treatment during pregnancy when around a third of women note worsening symptoms (111-113). Nonsteroidal anti-inflammatory drugs (NSAIDs) can be effective in reducing bone pain (114). The mast cell stabilizer cromolyn can also be used to reduce bone pain and GI symptoms (115, 116). In cases where neither leukotriene antagonists (as a second-line drug) nor cromolyn prove effective, omalizumab, a monoclonal antibody against IgE can be considered (117). For the effective systemic treatment of pruritus antihistamines may be given while second generation antihistamines may also be used in higher doses (57, 110). Finally, while focusing on reducing symptoms of mast cell degranulation it is important to also treat possible co-morbidities such as osteopenia, depression and vitamin D deficiency (7, 96, 118, 119).

In advanced forms of SM, symptoms are not only caused by mast cell degranulation but also by increased monoclonal mast cell infiltration (18). Such forms of SM thereby require treatment aimed at reducing neoplastic mast cell burden in addition to previously mentioned therapies (57). To date, two therapies for advanced SM subtypes have been approved in the United States by the FDA, namely imatinib and midostaurin (57, 120). Since D816V Kit causes resistance toward imatinib its use is limited to patients not carrying this Kit mutation (121). Midostaurin on the other hand is a tyrosine kinase inhibitor effective against D816V Kit (122). Around 60% of mastocytosis patients respond to midostaurin treatment (123). Both in ASM and MCL durable and improved survival has been demonstrated with such treatment, although relapses of the disease are frequent (18). Neither imatinib, midostaurin nor other targeted therapies in development are able to fully eradicate advanced forms of SM however (124). Thus, the final therapeutic option in such cases remains an allogenic hematopoietic stem cell transplant (HSCT) (125). A HSCT is only viable for younger patients with no further co-morbidities and a suitable stem cell donor (125). Results are better for ASM and SM-AHN patients than for MCL, however it remains a treatment of last resort with rates of progression free survival remaining low (18, 126).

To date no feasible curative treatment for the vast majority of mastocytosis patients exists. Treatment for symptom control, for severe cases of CM and ISM in particular (the main aim of treatment for these subgroups), is lacking in both efficacy and regulatory

approval. To evaluate and improve treatment efficacy, the highly variable and subjective concept of symptom severity of CM and ISM needs to be made measurable. A patient-reported-outcome (PRO) instrument is the preferred instrument for measuring patients' perceptions of symptoms, especially when these are highly individual and do not correlate with physiological parameters. Thus, there is a clear unmet need for a disease-specific symptom severity PRO instrument to facilitate future improvements to symptom control of CM and ISM.

As discussed previously, symptom reduction and improving quality of life for patients with mastocytosis is a central mainstay of therapy (17). It is therefore important to consider how concepts like symptoms of disease and quality of life evolved over time, and what methods are used to measure them.

4 Patient-reported Outcomes

Illness and patient care are not static concepts and how physicians have viewed these has changed radically over time (127). In the past, medical practice was guided by a disease-centered model of medicine, which emphasized the treatment of disease through a mechanistic understanding of body functions, guided by measurable indicators of success and using tried and tested therapies (128). Although this approach in many ways laid the groundwork of scientific break-throughs in medical science and vastly improved the standard of medical treatment, recent decades have seen a shift from the disease-centered model to a patient-centered model aiming to achieve a more holistic approach to patient care (127). To this end, pathophysiologic aspects of disease are complemented by psychological and social considerations to allow for more individualized evidence-based therapy (129). In patient-centered care patients are viewed as active and integral players in their own treatment being experts in their illness and their unique experience of being unwell (128). In order to take an individual's experience of illness into account in clinical trials and routine care, such experiences need to be made measurable (130).

Patient-reported outcomes (PRO) allow the measuring of unobservable or latent aspects of disease (127). A PRO is a report completed directly by the patient, without secondary interpretation, of how they feel or function as a result of the health condition or its therapy (131). While a PRO is often an umbrella term for the subject of measurement,

the instrument measuring it and the endpoints in clinical trials (127), this paper uses the terms items of interest, PRO instrument and PRO endpoints respectively.

The design of PRO instruments can vary considerably according to their purpose, and various response options are common (132). The Likert-scale for instance relies on the assumption that any patient response to a single object moves linearly along a single dimension (130). It thus entails an ordered set of response options from which a patient chooses the one that best describes his or her experience (132).

The use of PRO instruments has many advantages. Unlike patient interviews, the collection of a patient's subjective response to treatment using PRO instruments saves time and avoids a degree of interpretation by the collating physician, thereby reducing inter-observer variability (133, 134). In addition, PRO instruments allow results to be quantified making them more comparable (both in a time progression and between patients). By measuring aspects of disease and therapy that are only known to patients PRO instruments allow clinicians to better act according to the patient's needs and expectations, thus also potentially improving doctor-patient communication (131, 135). By being able to compare standardized PRO outcomes for patients at various times during treatment, PROs can improve patient satisfaction by allowing for more realistic expectations of therapy (136). When PRO instruments are integrated into disease treatment and monitoring, they allow healthcare providers to react to patient's needs and thus potentially increase the responsiveness of treatment to phases of disease activity. This can also make treatment more cost-effective (137). Concerning clinical research, having comparable PRO outcomes between patients allows PRO data to be analyzed on a population level, not just on an individual one. Thus, PRO instruments allow patient views to be included in clinical trials, not just case reports. PRO instruments are often used to measure a patient's response to treatment by comparing baseline scores with changes in PRO scores during a trial period (131, 138). They thus play a further important role in clinical research by providing more standardized data on a patient's perceived health during new treatments (139).

With importance of PRO instruments in patient-centered care widely recognized, regulatory bodies around the world have proceeded to endorse the use of PRO instruments in clinical trials (134, 140). For the United States Federal Drugs Authority (FDA), endorsement has been coupled with the formulation of higher standards in the development and evaluation of PRO instruments and outcomes (141). Under these higher standards claims made by PRO instruments are held to the same regulatory and

scientific standards as other measures used in clinical trials (131). As in other clinical fields, PRO instruments have become important in dermatology for clinical research and routine care (142, 143). Here, common concepts of interest include health-related quality of life (QoL), the measurement of symptom severity and treatment satisfaction (144, 145). In measuring these concepts of interest disease-specific PRO instruments have the advantage of being potentially more sensitive to change compared to more generic measures (146). The implementation of disease-specific PRO instruments is particularly useful for rare diseases like mastocytosis as they can be designed to provide statistically significant results with small sample sizes and are potentially responsive to minimal treatment effects (147). According to FDA guidelines care should be taken however to avoid drawing conclusions from PRO instruments solely based on statistical significance, since significant results sometimes result from minimal changes in PRO results that may not have clinical relevance (132).

It is important to differentiate between different types of concepts of interest measured by PRO instruments. While health-related quality of life instruments (a subset of quality of life instruments) such as the Mastocytosis Quality of Life Questionnaire (MC-QoL) measure the overall effect of illness on a patient in everyday life, disease activity focusses solely on a patient's clinical symptoms (148). Although the two concepts both form part of the multidimensional concept of disease, they are distinct and should be studied separately. Thus there is a need for a disease-specific disease activity score for mastocytosis, with the potential to better monitor current treatment regimens and assess benefits of new treatments during clinical trials (149).

The goal of this study was to test whether a new PRO instrument measuring the disease severity of mastocytosis, specifically of CM and ISM, could be designed and validated. This new PRO instrument is called the Mastocytosis Activity Score (MAS). The disease-specificity for adult CM and ISM patients would allow MAS to be applicable to the vast majority of adult mastocytosis cases while also simplifying validation in terms of required sample sizes. Although predominantly affecting children, about 10% of adult patients with mastocytosis suffer from CM without evidence of systemic involvement, thus presenting a considerable proportion of adult cases (150). Due to these mastocytosis subgroups having similar symptoms of cutaneous involvement and mast cell degranulation allowed for a combined PRO of symptom activity for ISM and CM patients. Furthermore, including CM patients would have the further benefit of allowing for the inclusion of patients with MIS.

Generally, generic QoL tools are not as responsive to change as disease-specific designs in dermatology (151). Therefore, the MAS remains of value even when two validated PRO instruments for mastocytosis already exist to date; the symptom severity score “Mastocytosis Symptom Assessment Form“ (MSAF), developed by Anrooi et. al., and the MC-QoL developed in conjunction with MAS. Unlike MAS, MSAF is disease-specific only to SM and hence was developed for a different population of interest. MC-QoL on the other hand was designed for a different concept of interest and uses retrospective data collection as opposed to the prospective measurement of MAS (149, 152). MAS with its population of interest being CM and ISM patients has the potential to be more sensitive to the impact of mast cell degranulation on mastocytosis symptom severity (151, 153, 154). Furthermore, there is currently still no instrument to measure the disease severity of mastocytosis in the German language.

5 Methods

Instrument development was guided by the intended target claim of MAS, namely that its total score was to show a current measure of and potential change in disease activity of CM and ISM (from a patient’s perspective). The concept of interest of MAS was thus defined as CM and ISM disease activity (132). For MAS to capture this concept of interest adequate content validity was required (155), being defined by FDA guidelines as empiric evidence that items and domains of an instrument are appropriate and comprehensive relative to its concept of interest, population and use case (132). Content validity is particularly important in dermatology where PROs can help improve patient-centered research (145). Good content validity is essential not only for the generalizability of results and the appropriateness of subsequent clinical decision-making, but also for ensuring adequate completion rates of the instrument itself (145). MAS instrument development thus needed to demonstrate that its final items and domain structure would capture the connection between disease activity and how the target population understood and discussed disease activity (155).

Having determined MAS’ concept of interest the instrument’s appropriateness hinged on how it was to measure said concept. This depended on its context of use (132), which was defined as future clinical trials and routine care of patients with CM and ISM. To prevent heterogenous and sporadic symptoms from being missed during routine clinic

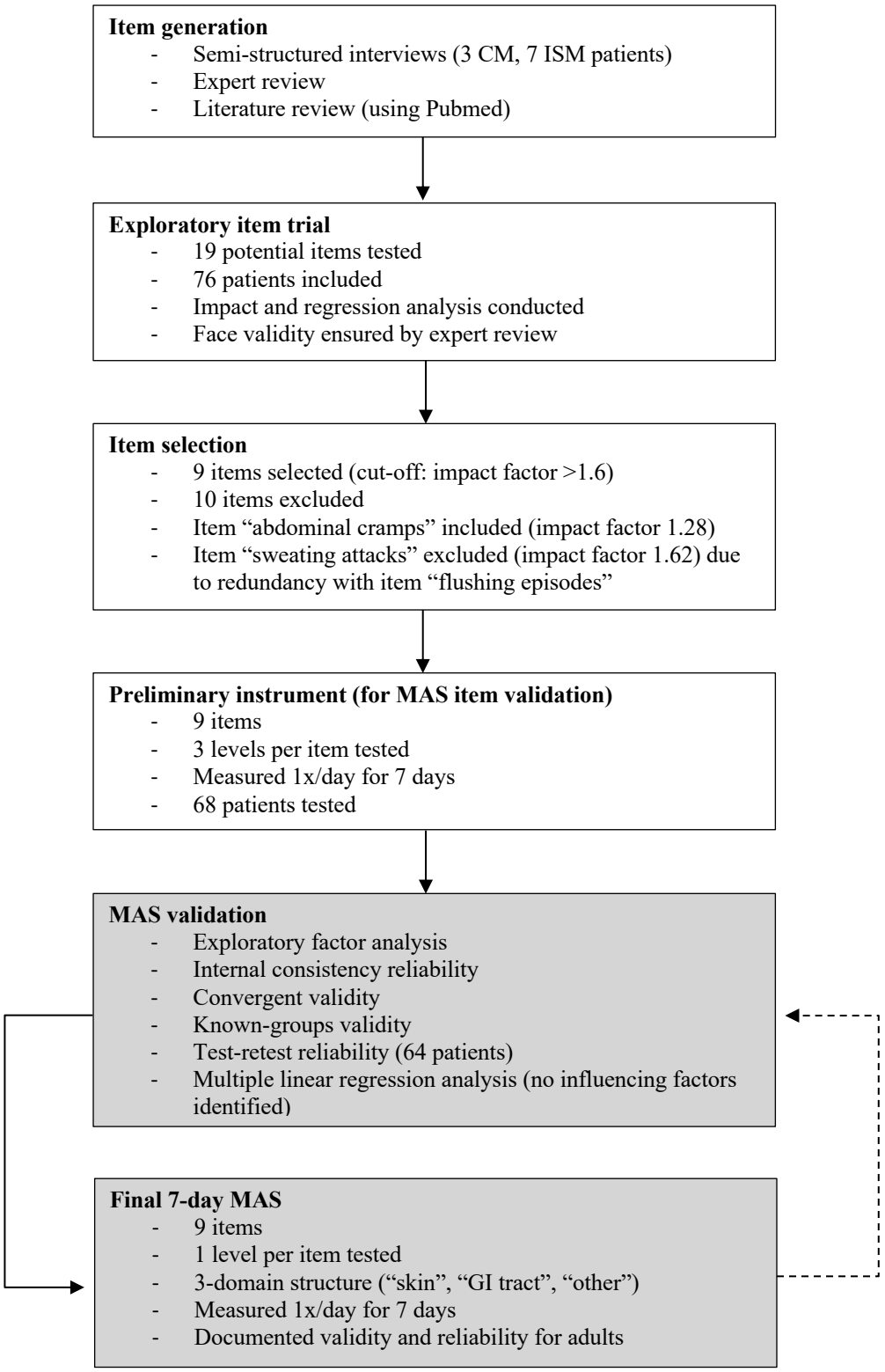
visits, MAS was designed to be administered once per day for seven days, each administered MAS entry thus recording a 24-hour interval. Since the content administered each day remained the same, MAS was given a degree of flexibility allowing for longer or shorter administration periods should the need arise. To facilitate frequent administration and to keep MAS' impact on patients' daily routines low, it needed to be self-administered. Thus, it needed to be easy-to-use and understandable for the target population by being as simple and concise as possible while retaining concept saturation.

Along with its concept of interest and its context of use, the appropriateness and content validity of a PRO instrument depended on its target population. Designed to be disease-specific, the target population of MAS was defined as patients with CM or ISM over 18 years of age. The exclusion criterion of <18 year-old patients took into account likely differing language comprehension and varying understanding of the concept of disease, thereby potentially requiring a separate PRO instrument for minors (137). The similar symptoms displayed by adult CM and ISM patients allowed for a single PRO instrument to measure disease activity for both subtypes. Including CM patients also allowed the evaluation of patients with an initial diagnosis of MIS. Thus, patients with confirmed mastocytosis with skin involvement, but unconfirmed possible bone marrow or systemic involvement were included in the target population. Patients included were not allowed to have other debilitating diseases as this would negatively affect external validity. A further exclusion criterion was the presence of more severe forms of SM. Taking the revised diagnostic criteria of 2016 into account, patients with SM-AHN and SSM were not included in the analysis and validation of MAS. Concept elicitation was carried out in German with a translation in English and a review for equivalence of content being performed after the German version underwent validation. The early stages of MAS development were performed in parallel to the development of the disease-specific MC-QoL instrument.

With definitions of important characteristics of MAS in place, instrument development was conducted. A systematic instrument development is essential for establishing content validity (155). To this end, qualitative and quantitative studies were conducted to identify, measure and evaluate items reported by patients. In line with current recommendations the development of MAS involved three main stages; item generation, item selection and instrument validation (153). As shown in Figure 2, each stage established a new version of the PRO instrument, which was improved upon during consecutive stages following analysis and review. This process resulted in the final

seven-day prospective MAS instrument. It must be noted that the development of any PRO instrument is iterative in nature so the resulting final MAS version represents the best version according to available PRO data of the population of interest to date (68).

Figure 2: Flowchart of Mastocytosis Activity Score (MAS) development (156)



This flow-chart highlights the major stages of the MAS instrument development process. Each stage of development (item generation, item selection, instrument validation) involved the testing of evolving combinations of potential items and measurement designs, culminating in the final 7-day MAS instrument design. The stage “MAS validation“ and the subsequent “Final 7-day MAS“ instrument design are grey, denoting the steps which were solely part of MAS development and not performed in combination with MC-QoL instrument development. The dashed line highlights the iterative process of PRO development and the continuing future validation and improvement of MAS design resulting from future data collection.
Abbreviations: CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; MAS, “Mastocytosis Activity Score“

5.1 Item Generation

Item generation followed a semi-quantitative approach using patient interviews, consultation of expert opinion and literature review. Item generation and preliminary concept elicitation was conducted via qualitative patient interviews. Following approval from the Charité Universitätsmedizin Berlin ethics committee (EA1/187/12) and consent of each patient, interviews were held via telephone using a semi-structured approach. The setting of individual interviews was chosen over that of a focus group in order to give each participant equally weighted time to discuss the concept of interest, thereby preventing discussions from being dominated by the most vocal individuals. Avoiding group settings further reduced the bias of individuals failing to discuss potentially sensitive and personal aspects of mastocytosis symptoms (132). Interviews were held with three CM patients and seven ISM patients to closely mirror the adult target population. Avoiding clinical or scientific terminology, the interview focused on open-ended, neutral questions concerning symptoms of mastocytosis. Each interview was performed by the same interviewer to reduce the risk of inter-interviewer variation. During each interview, the patient was also given the opportunity to freely brainstorm personal associations with the disease concept without being guided by interviewer questioning. Interviews during MAS instrument development were conducted in combination with the development of the disease-specific QoL instrument MC-QoL. For this reason, the interview stage also included questions regarding QoL along with an interview section focused on signs and symptoms of mastocytosis.

By way of induction, items mentioned in the initial interviews were included in the preliminary instrument (155). In combination with subsequent expert opinion and literature review, item generation followed an adaptation of grounded theory as recommended for PRO development (157). Concept saturation, the stage of data collection during which no further relevant information is elicited (158), was tested through further literature review on symptoms of mastocytosis along with a consultation of expert

opinion on further relevant items (156). In total, item generation produced 19 potential concepts before item saturation was reached. Expert opinion was gathered from dermatologists specialized in the treatment of mastocytosis. Said dermatologists specified overarching symptom-groups of interest, recommended instruments like the Likert-scales for standardized measurement and finally were involved in later item reduction. A Pubmed search focused on published data on mastocytosis-related symptoms. Along with examining concept saturation this literature review of the Pubmed database was in line with FDA (and other regulatory authorities) recommendations concerning PRO development (132, 154).

The 19 potential concepts were translated into items with three levels (symptom severity, frequency and duration of symptoms) and was administered to 76 patients with mastocytosis. Due to the simplicity and universality of the response form, a Likert-scale was chosen to measure the concept of disease (130). A 5-point Likert-scale for severity (0 – not at all; 1 – mild; 2 – moderate; 3 – severe; 4 – very severe) as well as 4-point Likert-scales for frequency (1-2; 3-4; 5-6; >6 times) and duration of symptoms (<1h, 1-6h, 7-12h, >12h within 24 hours) were created. All items were assessed daily over 7 days.

5.1.1 Data Collection during Exploratory Item Trial

The preliminary instrument was administered to 76 patients with mastocyotisis following approval by the Charité ethics committee and written informed consent of individuals. Of the 76 patients included in the exploratory item trial, 55 were female. The mean age of the population was 51.6 years (with a standard deviation of ±13.5 years). The trial population had a median age of 52.5 and a range of 20-77 years. All patients were recruited from the outpatient clinic of the Department of Dermatology and Allergology, Charité - Universitätsmedizin Berlin, Germany. The included patient population was over 18 years of age, either suffered from CM or ISM, and suffered from no further debilitating chronic diseases. Each item was measured for symptom severity, relevance and importance to allow for subsequent impact analysis. Item relevance was evaluated by asking whether the patient suffered from a specific symptom in the past 12 months (answer options: yes or no). Item importance, as perceived by patients, was determined using a five-point Likert-scale (1 = not important; 2 = less important; 3 = important; 4 = very important; 5 = extremely important). Patients were also asked to evaluate the completeness and clarity of MAS as well as add any further suggestions regarding the

MAS in an open comments section. In addition to an impact analysis, the completed potential MAS items allowed for an additional testing of face-validity.

5.2 Item Selection

Using data collected in the exploratory item trial, item selection involved a semi-quantitative approach through impact analysis of items and expert consultation. As a final result, item reduction produced the preliminary instrument for MAS item validation.

5.2.1 Impact Analysis

An impact score was created for each item of the exploratory item trial. The impact score constituted the product of mean importance of an item as judged by patients and the proportion of patients who experienced said item in the past 12 months (frequency). Higher impact scores denoted higher item impact. Items displayed impact scores ranging between 1.15 and 3.10.

5.2.2 Item Reduction

Following expert consultation, an impact score of >1.6 was determined as the best suitable cut-off in terms of face-validity for items to be potentially included in the preliminary MAS instrument. All items with an impact score below 1.6 were excluded. Before final inclusion, all items were also evaluated by the aforementioned expert panel to ensure content validity. Exceptions to the impact score cut-off were made on grounds of minimizing instrument length, difficulty of administration and impact on patients, while retaining as high a concept saturation as possible. The item “sweating attacks“ was discarded despite an impact score of 1.62 due to a redundancy with flushing episodes, an item with greater impact. Conversely, although the item “abdominal cramps“ scored 1.28 in measured impact, it was included due to its significance for content validity, face validity and concept saturation of the preliminary instrument.

5.3 Instrument Validation

Having completed item reduction, the 9 selected MAS items underwent a validation trial by way of a preliminary PRO instrument. Giving written informed consent, 68 patients from the Charité Dermatology outpatient clinic partook in this validation trial. The validation trial included one patient with SSM and two patients with SM-AHN on an exploratory basis due in part to revisions in the 2016 WHO classification system. These patients were not included in further numerical analyses. Participants were asked to answer the nine final items once per day for a period of seven days. This process was repeated after at least six weeks. To examine whether a single-level PRO-design of MAS was sufficient to measure disease activity, the preliminary instrument included two further exploratory levels for each item, namely frequency of symptoms and duration of symptoms. The two exploratory item levels were each measured using a 5-point Likert-scale. Symptom frequency was measured by the scale 0 (not at all); 1 (1-2 times); 2 (3-4 times); 3 (5-6 times); 4 (>6 times). Symptom duration in the last 24 hours was measured by the scale 0 (not in the last 24 hours); 1 (<1h); 2 (1 to 6h); 3 (7 to 12h), 4 (>12h). During collection of MAS item data a patient's age, gender and disease duration was also recorded. For further validation purposes patients also answered a 12-item Short Form Survey (SF-12), the MC-QoL instrument, a global assessment of mastocytosis-related quality of life and a global assessment of disease severity.

5.3.1 MAS Computation

To calculate a MAS score the response options of symptom severity were given values from 0 to 4 (0 = not at all, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). MAS was computed by cumulating the values of all item severity for all seven days to produce scores between 0 and 252 points. To better handle varying levels of item completion and duration of administration the sum of points was then translated to a scale from 0 to 100 to form the final total MAS score. Higher values constituted higher symptom severity of mastocytosis. Thus, the maximum score of the final MAS was 100 points. This allowed for better comparability between scores even in the presence of occasional missing data and allowed for potentially more flexible recall periods. An exclusion criterion for evaluating a final total MAS score was >25% missing items, requiring patients to

complete at least 48 of 63 total Lickert-scales in a 7-day time-span and having no more than 15 missing data points per 7-day MAS. The total score of items in each domain was later related to the number of non-missing items. Of the 68 compiled MAS instruments, three were excluded in the first 7-day period because each individual had >25% missing data points. Twelve patients were excluded due to >25% missing item responses in the second trial period.

5.3.2 Exploratory Factor Analysis

Using exploratory factor analysis, the relationships among the nine items of MAS were assessed and possible underlying structures or latent variables of the concept of interest were examined. Furthermore, exploratory factor analysis aided in the quantitative underpinning of content validity (132). Using the multivariate technique of principle component analysis, a component correlation matrix was calculated resulting from the linear correlations between all individual items. To this end, all factors and domains were required to have an eigenvalue of ≥0.5. Items were then grouped to the domain for which they exhibited the highest factor loading. To achieve greater clarity in comparing correlations and factor loadings, the matrix underwent rotation in the form of PROMAX oblique rotation. Finally, it was determined whether these groups were also consistent in terms of content and face validity by the expert working group.

5.3.3 Internal Consistency

Internal consistency is a measure of how closely PRO instrument items are related and thus shows how closely these items measure various facets of the same concept of interest (159). This is also more broadly an aspect of reliability (160). Cronbach's alpha is the most widely used measure of internal consistency when evaluating PRO instruments (159, 161). For MAS, the correlations between individual MAS items along with the homogeneity of both total and domain scores were thus measured. Following current common practice Cronbach’s alpha coefficient values between 0.8-0.9 were considered to have excellent consistency, >0.9 represented excessive consistency while <0.6 was deemed unacceptable consistency (132).

5.3.4 Convergent Validity

Convergent validity, an aspect of construct validity, assumes that the scores of two PRO instruments measuring similar or related concepts of interest should correlate highly with each other (162). To test MAS' convergent validity and provide further evidence for its construct validity, patients were asked to answer additional PRO instruments at two points during the MAS validation study, once during the first week and once at least six weeks later. The additional PRO instruments were selected for measuring related concepts of interest compared to MAS (mastocytosis symptom severity) and thus were postulated to display a strong correlation with MAS total and domain scores.

The following PRO instruments of reference, or anchors, were assessed in addition to MAS during the validation study: one patient global assessment (PGA) of disease severity, one PGA of quality of life, MC-QoL, and SF-12. Both PGAs were conducted using four-point Likert-scales. MC-QoL is a mastocytosis-specific health-related QoL questionnaire developed in parallel to MAS (152). This PRO includes 4 domains (symptoms, functioning/social life, emotions, skin) with 27 items in total and a two week recall period. Like MAS, MC-QoL scores were calculated for total and domains on a scale from 0 to 100 points with higher scores indicating greater impairment of QoL (152). The Short Form Survey SF-12, a shortened version of the 36-item Short Form Survey (SF-36), is a generic instrument assessing burden of disease (163). Its results are expressed in a physical component summary and a psychological component summary ranging from 0-100 points each, with higher scores indicating better self-reported health (164).

To correlate both the total score of MAS and its domain scores with the four anchors mentioned above a Pearson correlation was used. A Pearson correlation is a measure of the linear relationship between two continuous variables (165). It assumes the two variables in question have a straight-line relationship (166).

5.3.5 Known-groups Validity

Known-groups validity is demonstrated by an instrument's ability to discriminate between groups known to differ in the variable or concept of interest (167). It is thus a measure of whether scores of a PRO instrument reflect the known or hypothesized differences in levels of concept of interest displayed by different groups. In the case of mastocytosis with its high variability of symptoms, a second measurement of the concept of interest was conducted in the form of the PGA disease severity. With the assumption that both instruments measure similar concepts of interest, it was examined whether total MAS scores reflected the variation of results of PGA disease severity. Such known-groups validity would also support claims of construct validity (167).

5.3.6 Test-retest Reliability

The test-retest reliability is a measure of the stability of a PRO score when measuring a stable construct of the same person during two points in time (168). Thus, test-retest reliability was only examined for patients who completed the MAS score twice in an interval of at least 6 weeks. To better compare scores of both assessments, an intraclass correlation coefficient (ICC) was calculated. Unlike test-retest reliability which focuses on one individual over time, the ICC measures the degree of correlation or reliability between individuals that are similar regarding the concept of interest (169). Thus ICC can also be seen as the proportion of total unexplained variation in an outcome that is attributable to differences between the contexts of the construct (170). ICC values between 0.5 and 0.7 were defined to demonstrate moderate-to-good reproducibility of MAS results, while values >0.7 being considered to show excellent reproducibility (171, 172).

5.3.7 Multiple Linear Regression Analysis

To test whether certain patient traits significantly influenced MAS values, age (in years), gender and duration of disease (in months) were plotted as independent variables against total MAS scores (as the dependent variable) in multiple linear regressions.

5.3.8 Development of a US American English Version and Statistical Analysis

In order for MAS to be applicable to a wider range of patient populations, an American English (AE) version of the PRO was developed. This AE version can be found in supplementary figure 2. The translation focused on the conceptual equivalence to the German original rather than pure linguistic equivalence (173, 174). To this end two native AE speakers bilingual in German conducted independent forward translations of the German original MAS. Both translations were evaluated and merged by experts in the United States and then translated back into German by a German-AE bilingual native speaker. Finally, the backward translation was compared to the German original version by a German speaking expert panel and both German and AE experts agreed on a final AE consensus version.

SPSS (IBM SPSS Statistics version 22, IBM, Corporation, Armonk, NY, USA) was used for all statistical analysis as part of this study. A value $p < 0.05$ was defined to be statistically significant.

6 Results

6.1 Item Generation Results

Item generation, using semi-structured interviews of three CM and seven ISM patients, in combination with an expert review and literature review, produced 19 potential items for a CM- and ISM-specific symptom activity score. Following such preliminary questioning, the suitability of these items for such a future score was tested on a patient population of 76 patients in the course of the exploratory item trial.

6.2 Exploratory Item Trial

The 19 potential items of mastocytosis symptom severity were gathered by patient interviews, expert review and literature review until concept saturation was obtained. These potential items were then tested for perceived impact, importance and relevance by the 76 mastocytosis patients with CM or ISM (55 females; mean age 51.6 ± 13.5 (SD)

years, median: 52.5, range 20-77) in the exploratory item trial. Table 5 shows the results of the exploratory item trial as the mean “frequency“, mean “importance“ and resulting impact score of the 19 potential items.

Table 5: Impact scores of potential MAS items

Item	Mean importance	Relevance	Impact score
Itching	3.33	0.778	2.59
Skin redness	3.51	0.883	3.10
Flush episodes	3.02	0.559	1.69
Diarrhea	2.76	0.583	1.61
Nausea	2.50	0.458	1.15
Flatulence	2.62	0.525	1.38
Abdominal cramps	2.48	0.517	1.28
Fatigue	3.05	0.770	2.35
Palpitation	2.82	0.559	1.58
Sweating attacks	2.64	0.614	1.62
Dyspnea	2.58	0.475	1.23
Dizziness	2.73	0.508	1.39
Headache	2.74	0.600	1.64
Muscle or joint pain	2.97	0.705	2.09
Difficulty in concentrating	2.88	0.593	1.71
Hot flushes	2.54	0.576	1.46
Forgetfulness	2.52	0.550	1.39
Mood swings	2.47	0.607	1.50
Hypertension	2.61	0.534	1.39

Impact analysis was conducted by calculating an impact score for each potential item, determining their inclusion according to a cutoff of >1.6 impact score and subjecting them to a final expert review for increased face validity. In bold, the 9 selected final MAS items are shown. Impact scores >1.6 are italic. Mean importance was the mean score of a Likert-scale of item importance across the entire trial population. Relevance was calculated as the proportion of the trial population which experienced a given item content in the last 12 months. The impact score of each item was the product of mean importance and relevance scores.

Following impact analysis and an expert review, nine items were selected as final MAS items. These were then incorporated into a preliminary instrument which included all final elements of MAS as well as MC-QoL instruments. Validation and subsequent final adjustments to the MAS instrument design were conducted separately from the MC-QoL instrument development.

An impact score of 1.6 was determined as the impact cut-off by the expert working group as best suitable for face validity, with items of an impact >1.6 being included as final MAS items. In total, nine items had impacts >1.6, ten did not meet the cut-off. Following a final review of all items by the expert working group, two exceptions were made. “Sweating attacks” with an impact score of 1.62 was excluded due to redundancy with the item “flushing episodes”. “Abdominal cramps” was included with an impact score of 1.28 in order to improve face validity and concept saturation. Thus, the preliminary instrument along with the final MAS version included nine items in total.

6.3 Preliminary Instrument Results

Table 6 illustrates clinical and demographic details of the 68 patients that partook in the testing of the nine MAS items selected for the preliminary instrument. Taking the altered 2016 diagnostic criteria into account, patients with more severe forms of SM or those with too few completed MAS items were excluded from further analysis.

Table 6: MAS validation study sample group characteristics

	n	%
Gender		
Female	51	75.0
Male	17	25.0
Age		
18-30 y	5	7.4
31-50 y	19	27.9
51-70 y	37	54.4
>70 y	7	10.3
Diagnosis		
Cutaneous mastocytosis	17	25.0
Prediagnosis mastocytosis in the skin (Mastocytosis in the skin)	13	19.1
Indolent systemic mastocytosis with cutaneous manifestations	28	41.2
Indolent systemic mastocytosis without cutaneous manifestations	7	10.3
Smoldering systemic mastocytosis	1	1.5
Systemic mastocytosis with associated neoplasm (SM-AHN)	2	2.9
Duration of mastocytosis (in years)		
<5 y	13	19.1
5-10 y	28	41.2
11-20 y	18	26.5
>20 y	9	13.2

Abbreviations: n, number of patients; y, years; SM-AHN, systemic mastocytosis with associated non-mast cell neoplasm

6.4 Exploratory Factor Analysis Results

After data of the 68 patients was obtained an exploratory factor analysis was performed using the nine MAS items of the preliminary instrument. Results of this investigation are shown in Table 7. This process suggested a three-domain structure, thereby explaining 78.8% of variance in the results.

Table 7: Domain structure of MAS and factor loading of its items (156)

Item	Factor 1 (skin)	Factor 2 (gastrointestinal tract)	Factor 3 (other)
Itching	**0.936**	-0.103	-0.017
Skin redness	**0.822**	0.020	-0.108
Flush episodes	**0.561**	0.071	0.224
Diarrhea	-0.060	**0.946**	-0.073
Abdominal cramps	0.030	**0.817**	0.065
Muscle or joint pain	0.245	0.134	**0.539**
Fatigue	-0.071	0.021	**0.922**
Headache	0.040	0.031	**0.669**
Difficulty in concentrating	-0.084	-0.124	**0.994**

Using exploratory factor analysis a three-domain structure within the final nine MAS items was found. Each item was grouped into one of these domains (“skin”, ”gastrointestinal tract”, ”other”), for which the highest factor-loading (in bold) was ascertained.

Each of the three domains found was named after their dominating content: “skin“, “gastrointestinal (GI) tract“ and “other“. All items presented a high factor loading for only one of the three domains making it possible to clearly assign items accordingly. During a further review by the expert working group no changes to domains and groupings were deemed necessary.

6.5 Internal Consistency Reliability

Table 8 shows Cronbach's alpha, a measure of internal consistency, for the established domains and the MAS total score. With Cronbach's alpha of 0.85 for the total MAS score MAS demonstrated internal consistency. In addition, such internal consistency shows the appropriateness of the total MAS score. Cronbach's alpha values were >0.8 for all domains suggesting more than acceptable internal consistency.

Table 8: Internal consistency as measured for domain and total scores of MAS (156)

Domain	Items of the domain	Cronbach's alpha
Skin	Itching Skin redness Flush episodes	0.83
Gastrointestinal tract	Diarrhea Abdominal cramps	0.86
Other	Muscle or joint pain Fatigue Headache Difficulty in concentrating	0.86
Total MAS score		0.85

6.6 Mastocytosis Activity Score (MAS) Results

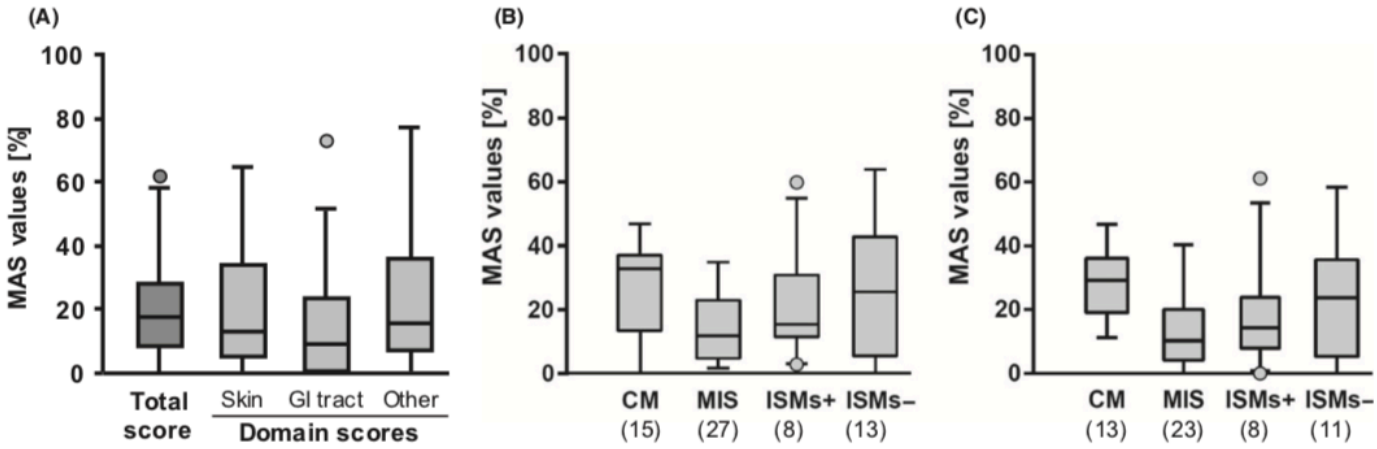
After determining the MAS domain structure and ascertaining its internal consistency, MAS total scores and MAS domain scores were analyzed. Figure 3 shows the distribution of the scores (of the preliminary instrument) among the population investigated. The scores are displayed as percentages of the highest attainable score (taking missing data into account) for the total score and individual domain scores. The box-plots show that domains have a broad range, but comparable median scores with values from 10 to 20%.

The mean values of the total MAS score ± the standard deviation (SD) meanwhile are as follows: mean of total MAS scores 19.5 ±14.5, of the "skin" domain 19.5 ±17.9, of the "GI-tract" domain 14.1 ±16.7, and of the "other" domain 22.2 ±20.1. The domains

have similar mean values as they show a range of only 8 points out of 100. The SD of the scores show that domain scores individually have a large but acceptable spread of data for patients during treatment.

Although there was significant variation in results between the mastocytosis subtypes in the first week of instrument testing (n=63, ANOVA, *P*=0.02), six weeks later there was no significant difference detectable (n=55, ANOVA, *P*=0.16). When analyzing the distribution of mean total MAS scores for disease subgroups in the second week of the study (as shown in Plot C of Figure 3), only patients who adequately completed the preliminary instrument with the final MAS items were included in later analysis.

Figure 3: Distribution of Mastocytosis Activity Score (MAS) Results (156)



Box-plots of total MAS scores and domain scores as ascertained during the preliminary instrument study phase. In Plot A median scores (both total and domain) are well-balanced. In Plot B total MAS scores of the first week of measurement, organized into mastocytosis subgroups are less well balanced, yet acceptable. In the first week, significant differences between the subgroups were found (B, n=63, ANOVA *P*=0.02). In Plot C, the total MAS scores of the second week of measurement does not display significant differences amongst subgroups (C, n=55, ANOVA *P*=0.16). Brackets display the total numbers of patients per subgroup.

6.7 Convergent Validity

Convergent validity was examined by correlating total and domain scores of MAS with results of the anchor instruments PGA disease severity, PGA QoL, MC-QoL, and SF-12 (SF-12 being split into mental component and physical component summary). As can be seen in Table 9, correlations are significant and in the expected direction. Convergent validity is strengthened by MAS and anchor scores having positive

correlations with Pearson's correlation coefficients of r = >0.5. MAS and SF-12 showed a strong negative correlation with a Pearson's correlation coefficient of r = <-0.5 due to opposite scoring scales.

Table 9: Correlations between MAS scores and other anchor instruments

	total MAS score	domain "skin"	domain "gastrointestinal tract"	domain "other"
PGA Disease severity	0.751 (p<0.05)	0.615 (p<0.05)	0.390 (p<0.05)	0.642 (p<0.05)
PGA QoL impairment	0.676 (p<0.05)	0.495 (p<0.05)	0.340 (p<0.05)	0.622 (p<0.05)
MC-QoL				
Total score	0.876 (p<0.05)	0.581 (p<0.05)	0.462 (p<0.05)	0.837 (p<0.05)
Symptoms	0.824 (p<0.05)	0.433 (p<0.05)	0.423 (p<0.05)	0.868 (p<0.05)
Emotions	0.568 (p<0.05)	0.373 (p<0.05)	0.344 (p<0.05)	0.527 (p<0.05)
Social life/ Functioning	0.774 (p<0.05)	0.489 (p<0.05)	0.450 (p<0.05)	0.739 (p<0.05)
Skin	0.711 (p<0.05)	0.896 (p<0.05)	0.196	0.470 (p<0.05)
SF-12				
MCS	-0.524 (p<0.05)	-0.283 (p<0.01)	-0.365 (p<0.05)	-0.512 (p<0.05)
PCS	-0.645 (p<0.05)	-0.419 (p<0.05)	-0.281 (p<0.01)	-0.652 (p<0.05)

Abbreviations: PGA, patient global assessment; MCS, mental component summary; PCS, physical component summary; MAS, Mastocytosis Activity Score; SF-12, 12-Item Short Form Survey.
Correlations between the total and domain MAS scores and each four-anchor instrument (PGA disease severity, PGA QoL impairment, MC-QoL and SF-12) are calculated as Pearson's correlation coefficients. Low scores in SF-12 and high scores in MAS represent increased QoL impairment. Thus, the correlation between these two scores is negative.

6.8 Known-groups Validity

Table 10 shows mean total MAS values as they relate to PGA disease severity. A patient's response to the PGA disease severity was compared to the MAS total values of the same week. PGA disease severity was used to group patients into four levels of disease severity. The total MAS scores discriminated well between these groups. As shown in Table 9, there was a positive correlation between increasing total MAS score and PGA disease severity. The interquartile ranges of total MAS scores for the different disease severity groups do not significantly overlap. Thus, MAS total values are able to differentiate well between groups of different disease severity.

Table 10: Total MAS scores of groups with varying disease severity

PGA disease severity (regarding previous 2 weeks)	n	MAS total value mean ± SD (median)	1st quartile	3rd quartile
(0) None	3	2.9 ± 5.0 (0)	0	4.4
(1) Mild	34	11.0 ± 6.9 (10.3)	5.7	16.4
(2) Moderate	20	28.1 ± 8.8 (26.6)	21.7	34.7
(3) Severe	8	42.4 ± 12.8 (41.3)	33.3	49.7

Total MAS scores as grouped according to patients' response to PGA disease severity. The values of the PGA disease severity Likert-scale are shown in brackets.

6.9 Test-Retest Reliability

In total, 55 patients gave responses adequate for the evaluation of test-retest reliability. Table 11 shows the mean values of the first assessment with those of the assessment at least six weeks later. The results display minimal variation between the two assessments. The relatively small range of mean domain values from 14.1 ("GI-tract") to 22.9 ("other") suggests patients on average are affected evenly by all three domains of the instrument. An intra-class correlation coefficient of 0.91 for the total MAS value and >0.8 for the domains "GI-tract" and "other" suggests excellent reproducibility. Only the domain "skin" displayed an intra-class correlation of 0.75, which indicates lower but acceptable reproducibility. A slightly lower intra-class correlation in the domain "skin" may be due to a more rapid fluctuation of skin symptoms in general. Another possible

explanation is the inclusion of the two items with the highest impact score, “itching” and “skin redness”, in the domain “skin”. Patients may possibly place a greater importance on these items and as a result be more sensitive to small changes in them. As displayed in Figure 3, a significant variation in the distribution of MAS scores of the different disease-subgroups was found for the first trial period, but not the second.

Table 11: Test-retest reliability for final MAS items

MAS scores	Mean score ±SD (median score) - 1st assessment	Mean score ±SD (median score) - 2nd assessment	ICC
Total score	19.8 ±14.4 (17.9)	21.0 ±15.2 (18.9)	0.912
Skin	19.4 ±17.7 (13.7)	20.4 ±16.0 (19.1)	0.749
GI-tract	14.1 ±16.6 (8.0)	15.7 ±18.1 (12.5)	0.866
Other	22.9 ±20.2 (18.7)	24.1 ±20.7 (19.6)	0.942

A subsample of 64 patients answered MAS sufficiently, the 2nd assessment commenced at least six weeks following the first. ICC (intraclass correlation coefficient) values of >0.7 throughout indicate respectable reproducibility.

6.10 Factors Influencing Total MAS Scores

Possible factors influencing total MAS scores, namely gender, age and disease duration were compiled along with the 9 final MAS items. A multiple linear regression analysis was conducted between these factors and the total MAS scores. Table 12 shows the results of this multiple linear regression analysis. None of the three recorded factors was shown to have a significant influence on total MAS scores.

Table 12: Possible factors influencing total MAS scores

	Unstandardized Coefficient B	Standard error	P-Value
Age (years)	-0.024	0.142	0.864
Gender	-7.366	4.301	0.093
Disease duration (months)	0.003	0.019	0.876

6.11 Multiple Linear Regression Analysis and Item-level Structure

A Pearson's correlation of results between symptom frequency and symptom severity, as well as between symptom duration and symptom severity was used to examine the need for a multi-level item design for the final MAS instrument. As seen in Table 13, very high correlations between both symptom frequency and symptom severity, as well as between symptom duration and symptom severity were found for all MAS items. Thus, it was determined that the final MAS as a single level instrument of symptom intensity would be adequate and more efficient than a multilevel approach in monitoring overall disease severity.

Table 13: Correlations within the preliminary multi-level MAS design

Correlation between symptom frequency and duration with intensity respectively		
Symptom	Correlation of symptom intensity and symptom frequency	Correlation of symptom intensity and symptom duration
Itching	0.91	0.92
Wheals	0.89	0.86
Flush episodes	0.92	0.92
Diarrhea	0.94	0.89
Abdominal cramps	0.94	0.93
Muscle or joint pain	0.91	0.92
Fatigue	0.90	0.91
Headache	0.89	0.89
Difficulty concentrating	0.89	0.92

Symptom frequency and duration both showed a high correlation with symptom severity for all symptoms measured in the preliminary multi-level MAS design. Based on such high Pearson's correlation, these two item levels were thus deemed to be redundant and were excluded from the final MAS design. Correlations among the levels were highly significant with P-values smaller than 0.001 throughout. Table 13 displays correlation values between symptom frequency and intensity, as well as between symptom duration and intensity.

With multiple regression analysis completed, the final MAS instrument design was determined to be a seven-day, prospective and single-level instrument made up of nine items. Upon finalizing the MAS design the PRO was translated into a US American English version as detailed previously. Appendix A and B shows the final German and US American English language versions of the seven-day MAS.

7 Discussion

Mastocytosis can have a very debilitating effect on a patient's health-related QoL (57, 175). What is more, a patient's symptoms of Mastocytosis seldom correlate with physiological parameters, thus frequently rendering these inadequate as markers of disease severity. Making the disease more measurable would thereby greatly improve our understanding of mastocytosis disease severity and could potentially lead to improved QoL through better treatment. PRO instruments offer a valuable tool for measuring disease severity by bypassing the measurement of physiological parameters for the direct measurement of individually perceived symptoms. With current PRO instruments still lacking in specificity and/or suitability, there is a need for the development of disease-specific instruments to better measure the disease activity of Mastocytosis. The development of the Mastocytosis Activity Score fills a gap in the mastocytosis research toolkit and thus represents a valuable instrument for improving both future treatment and clinical research of the disease.

The development of MAS involved an iterative process of patient interviews, probative instrument administration, expert consultation and literature review. Through concept elicitation, item generation and item selection, the final nine items of MAS were determined as seen in Supplementary Figures 1 and 2. During the item generation phase three patients with CM and seven patients with ISM completed semi-structured interviews. Although the format of semi-structured interviews offered many advantages, time constraints limited the number of patients interviewed. A larger number of patients would have been preferable, potentially providing a wider and more nuanced array of responses. The distribution of CM and ISM patients in the item generation phase however reflected the greater prevalence of ISM in the adult population.

The subsequent exploratory item trial allowed for item reduction, while an instrument validation study allowed for the validation of the final nine items and the determination of the final structure of MAS. Although the sizes of both trial populations

could have been larger, they nevertheless significantly improved upon the item generation phase. Both trial populations however suffered from a gender imbalance toward female participants, with only 27.6% and 25% being male. This is most likely a chance occurrence due to the low prevalence of mastocytosis in the population as a whole and the decision to recruit the trial populations from only the patient pool of one university treatment center. The discrepancy between the gender distribution of the trial population and the population of mastocytosis as a whole is a marked limitation of the results of the validation studies. This only further highlights the need for an iterative design process and further validation as more data becomes available.

MAS is a prospective self-administered, nine-item, three-domain and single-level disease activity score, specific to CM, MIS and ISM. The total score of MAS provides a measurement of disease activity, while its three domains (“skin“, “gastrointestinal-tract“, and “other“ symptoms) allow further differentiation of the nature of that disease activity. With the help of the validation study the newly designed MAS was found to demonstrate both high validity and reliability.

The instrument design, created with the help of expert-group consultation, contributes to the content validity of MAS. The Likert-scale was used for its simplicity and flexibility. This makes MAS easier for the patient to understand and quicker to administer, thereby potentially increasing recall. In addition, Likert-scales are very common in PRO instruments, potentially increasing the number of patients who are already familiar with its structure. MAS questions were designed to avoid redundancies and to make questions as neutral as possible, thereby avoiding unintentionally influencing patients’ answers and reducing acquiescence bias. The use of Likert-scales also allowed for greater flexibility both in experimenting with various item level designs and in the duration of administration (a seven-day period was ultimately chosen), while retaining the overall MAS structure. The assumption underlying the Likert-scale, that response options are evenly spaced, made the calculation of total and domain MAS scores possible. It also simplified and accelerated interpretability while proving useful for managing missing data. Scaling total scores furthermore facilitated comparisons between the three domains. Choosing a five-point Likert-scale for each item strikes a compromise between providing enough answer options to allow for differentiated responses and keeping instrument length manageable. If PRO instruments become too long the accuracy of patient responses decreases, thus reducing their validity (130). MAS also took advantage of the fact that including multiple items dilutes any impact of random error of one particular item (130).

It is important to consider Likert-scales` shortcomings when analyzing MAS results. In order for MAS to make latent variables of disease activity explicit (along with its domains) it needed to introduce semi-quantitative response options (“not at all” to “very severe”). The interpretation of such response options can vary from patient to patient and for an individual over time. Thus, it is not possible to precisely determine whether MAS response options are interval or just ordinal (130). For example, it cannot be said with certainty that a patient who has twice the total MAS score as before suffers from twice the disease activity. The advantages of the Likert-scale however outweigh its drawbacks, since MAS as a multi-item instrument allows for a more accurate measurement of its latent concept of interest.

A second issue related to MAS design is the order in which response options were presented. Since all options were presented in order of “not at all” to “very severe”, MAS design suffers from the possibility of acquiescence bias. Thus, even if a patient selects the most extreme response options for all items, there remains the possibility that this rather one-sided ordering of responses influenced the individual. To alleviate this, response options could have been listed in random order. Furthermore, response-options all pertain to the “presence” of symptoms rather than the “absence” of symptoms, possibly skewing a patient’s interpretation of the scale. Both such aspects of the MAS scale were however accepted in favor of retaining simplicity, improving recall and increasing accuracy of responses. It is important to note that MAS response options do not take the form of “agree”-“disagree” scales, but rather frame responses in order to best describe aspects of the latent concept of interest.

The careful instructions of MAS recall of “once daily in the evening over the last 24 hours on 7 consecutive days”, provides several advantages to the MAS instrument. Instructing on administration “once daily in the evening” is precise enough to ensure similar recall intervals, while giving the patients a degree of flexibility to allow easier administration and reduced impact on everyday-life. Daily recall periods were chosen to account for the highly variable occurrence of symptoms in mastocytosis. FDA guidelines suggest keeping recall periods as short as possible (132), however event-driven recall was deemed too intrusive for patients filling out the MAS. A recall on “7 consecutive days” was aimed at combining the advantages of shorter and longer recall periods, thus covering short-term symptoms and longer-term changes in symptom activity. Furthermore, this week-long recall ensured the documentation of symptom severity during weekends, thus mitigating possible effects of work or recreation on average MAS

scores. In contrast, the fortnightly recall of MC-QoL is better suited to longer-term changes in its concept of interest, as in retrospective study designs, but is less effective measuring short-term symptoms. The design of MAS for both routine care and clinical trials was also reflected in the use of language. Simple, everyday terms made MAS easy to understand to improve recall and allowing for self-administration. Administration by clinical professionals and use in clinical trials was taken into account by also including technical terms to reduce ambiguity of MAS items.

The use of language also plays an important role in the concept validity of MAS. The instrument was designed solely in a German language and cultural context. The subsequent US-English translation plays a vital role in making the instrument accessible to a greater patient population and allows it to be tested and reviewed by the greater scientific community. Analyzing a US-English version of MAS in the earliest stages of MAS development of item-generation, -selection and -reduction, would potentially have made the version's content validity even more promising. In the future, it is hoped that the US-English MAS version will undergo its own testing for reliability and validity. This would also further the validity of the German original version by providing more information as to how language and cultural context of administration influences MAS scores. Further language translation, as for example the recent translation of MC-QoL into Spanish (176), and cultural adaptations would no doubt improve MAS applicability internationally.

Exploratory factor analysis found a three-domain structure within the nine MAS items. All items had a high factor loading for only one the three domains making a clear allocation to domains according to high factor loading possible. This enabled MAS to not only provide information on disease activity through the total MAS score, but also shed light on the quality of disease activity in terms of the three MAS domains. It also suggests that the patient experience of disease activity is primarily focused around the concepts of cutaneous symptoms and gastrointestinal symptoms, the domain "other" being not further divisible. Although the final 9-item MAS design has the advantage of being simple and quick to administer, having more the 9 items would possibly have allowed for a further divisibility of the domain "other". Exploratory factor analysis would have been preferable with a larger sample population as it diminishes error in the data set (177).

Total and domain MAS scores displayed high levels of internal consistency reliability. The value of Cronbach's alpha for total MAS scores was 0.85 indicating good internal consistency. This value can however be skewed due to Cronbach's alpha assuming that instruments have a single-domain or concept of interest, according to the

tau equivalent model (178). Furthermore, the number of items can also influence Cronbach's alpha values for total instrument scores. For this reason, Cronbach's alpha values of the three domains were also tested and support the good internal consistency of MAS. This property of the MAS score however only pertains to the specific population tested. Thus, investigators in future trials should be advised to always recalculate Cronbach's alpha for internal consistency reliability for their individual study populations and not rely solely on the above reliability estimates (179).

Due to the relatively small range of mean domain values from 14.1 ("GI-tract") to 22.9 ("other"), MAS results suggest that patients on average are affected evenly by all three domains of the instrument. In both the first and second weeks of the validation trial, the mean domain scores for "GI-tract" remained the lowest of the three. One possible explanation for this is that the GI-tract domain may have had the least effect on the QoL of the trial population. GI symptoms may also fluctuate more or with a lower frequency than other symptoms. Possibly GI symptoms are generally less severe or are better treated compared to other symptoms in mastocytosis. This does not mean that the GI-tract domain is the least significant, since the domain "other" merely grouped items due to indivisibility during factor analysis. Such analysis would be further corroborated with further MAS trials of intervals >6 weeks in length.

MAS total and domain values displayed large distributions as seen in the standard deviation of each in relation to their respective mean scores. Given the nature of the domain "other", it is unsurprising that it shows the largest SD of all domains and the broadest distribution of domain scores. Total and domain scores generally had a very broad distribution. This echoes the great variability and diversity of symptoms in the CM, MIS and ISM patient population. In examining the results of the first and second week of measurement, CM seemed to have the highest total scores during both weeks with high median total MAS scores and a comparatively small interquartile range. This may reflect the slightly high domain scores of "skin" compared to "GI-tract", however it is unclear whether this results from cutaneous symptoms having a larger impact on patients' concepts of disease severity.

To test for convergent validity, MAS total and domain scores were correlated with four anchor instruments. MAS total scores show significant correlations between all total scores of anchor instruments, indicating a good convergent validity. Particularly PGA disease severity, PGA QoL impairment and MC-QoL total scores show strong correlations of 0.676 to 0.876. As expected, PGA disease severity had a higher correlation with MAS

than PGA QoL impairment, due to the concept of interest of PGA disease severity being closer to that of MAS. Likewise, the high correlation between MC-QoL and MAS total scores is explained by the fact that both include similar items, however in differing modes of assessment. Within MC-QoL, the “symptoms” domain, which includes these items, has the highest correlation with total MAS score (Pearson’s correlation of 0.824). A high correlation (r= 0.896) between the MC-QoL domain “skin” and the MAS “skin” domain can also be explained by parallels in the concept of interest of each. The lowest correlation with total MAS scores was obtained by the mental component summary (MCS) of SF-12 with -0.524 Pearson’s correlation. Together with the -0.645 Pearson’s correlation of the physical component summary (PCS) of SF-12, this is still an acceptable and significant correlation, however it reflects MAS` focus primarily on physical symptoms of mastocytosis. Note that MCS and PCS of SF-12 show a negative correlation with MAS total scores due to higher disease activity being denoted by higher values in MAS and lower values in SF-12 scores. As MAS instrument development heavily involved patient interviews and self-administration of test items, the structure of MAS and its correlations with SF-12 components suggests that physical symptoms of mastocytosis play a greater role in patients’ perceptions of disease activity and symptom severity than mental aspects of the disease. Overall, MAS thus displays significant Pearson’s correlations with anchor instruments and so shows good convergent validity.

Known-groups validity, the ability to distinguish different patient groups, was tested by comparing the individual PGA disease severity scores with MAS scores of the same patient. The mean total MAS scores followed the expected positive correlation with PGA disease severity scores. The ability to group MAS total scores into broader levels of disease severity may aid in the interpretation of total scores in routine clinical care. Of the four response options of PGA disease severity, the interquartile ranges of “moderate” (21.7-34.7) and “severe” (33.3-49.7) did not significantly overlap. Other interquartile ranges did not overlap suggesting good known-groups validity.

Test-retest reliability was established by administering the final MAS items to each patient twice in an interval of at least six weeks. All patients included were deemed to have a stable disease and no changes to therapy were undertaken during the trial interval. With intraclass coefficients for total and domain scores all being >0.7, MAS was found to have excellent reproducibility. Although there is a large range of scores during both the first and second assessment, mean results were well balanced. The distribution of total MAS scores for the different mastocytosis subtypes was statistically different in the first

assessment, but not in the second assessment. This suggests that MAS performs better at distinguishing classes of disease severity, rather than distinguishing between mastocytosis subtypes. MAS thus performs according to its intended design. A possible explanation for the difference in distributions between the two trial periods is the high variability of symptoms and symptom severity for all mastocytosis cases. It is possible that different disease subgroups show differing levels or frequency of fluctuation in disease severity, even amongst patients undergoing treatment. By demonstrating excellent reproducibility, MAS' test-retest reliability is further supported.

Multiple linear-regression analysis furthermore did not find total MAS scores to be influenced by factors of age, disease duration or gender. None of these factors demonstrated a significant correlation with total MAS results with P-Values 0.093 or higher. Thus, these factors do not need to be taken into consideration when evaluating MAS scores, as long as conditions of old age do not inhibit self-administration.

There are further important aspects to be considered when evaluating the validity of MAS. To counter possible skewing of the MAS development process through strict development in one specialized center in the German cultural and language context, MAS must still be tested for its validity in different levels of patient care. The mean total MAS scores of various mastocytosis subgroups as well as the mean domain scores all displayed values <50 points. This likely reflects the effects of continuous treatment during the trial period. To establish minimal clinically relevant differences in MAS scores and examine the responsiveness of MAS to changes in treatment requires further testing. Although MAS was tested with one SSM and two SM-AHN patients on an exploratory basis, further testing and possible adjustments would be required to ensure MAS accurately measures disease activity in these subtypes. Crucially, important signs and symptoms of more severe types of mastocytosis may differ due to the presence of mast cell tissue infiltration and possible organ dysfunctions. These were not included in the CM-, MIS- and ISM-specific design of MAS, thus possibly making a disease-specific PRO for SSM and SM-AHN necessary in the future. The exploratory results of SSM and SM-AHN patients in the MAS validation phase were excluded in further calculations, thus they did not affect the validation of MAS for CM, MIS and ISM patient groups. MAS design also needs to be adjusted for use with patients below the age of 18. In line with the iterative nature of MAS development, further adjustments according to specific mastocytosis populations, language areas and cultural contexts can and should be undertaken.

8 Conclusion

In conclusion, this study documents the development of a validated and reliable disease-specific PRO instrument for disease activity of CM and ISM, including MIS. MAS has the potential to be expanded to versions beyond the German and US-American English cultural and language context, allowing for its use in multinational, multi-center trials. MAS thus is an important new tool in improving routine care of patients and furthering clinical studies on efficacy and regulatory approval of medication specific to mastocytosis.

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Supplementary Material

Supplementary Figure 1. German version of MAS

Mastozytose-Aktivitäts-Score – MAS

Anleitung: Bitte schätzen Sie einmal täglich abends die Schwere Ihrer mit der Mastozytose-Beschwerden über die vergangenen 24 Stunden an 7 aufeinander folgenden Tagen ein. Bitte geben Sie für jede der Beschwerden nur eine Antwort pro Tag an.

		Wie schätzen Sie die Schwere ihrer heutigen Beschwerden ein?							
	Tag	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Juckreiz	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Rötungen und Schwellungen der Haut (Quaddeln)	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Errröten des Gesichtes mit Hitzegefühl (Flush-Episoden)	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Diarrhoe (Durchfall)	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Bauchschmerzen	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Gliederschmerzen (Muskel- oder Gelenkschmerzen)	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Müdigkeit/Abgeschlagenheit	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Kopfschmerzen	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Konzentrationsschwierigkeiten	gar nicht	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
									Total MAS (0-252) ___ ___ ___

Supplementary Figure 2. US American English version of MAS

Mastocytosis Activity Score – MAS

Instructions: Please assess the severity of your symptoms associated with mastocytosis once daily in the evening over the last 24 hours on 7 consecutive days. Please select one of the five answers for each symptom per day.

		How do you assess the severity of your today's symptoms?							
	Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Itching	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Skin redness/swelling (wheals)	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Sudden feeling of warmth and reddening of the face (Flush episodes)	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Diarrhea/loose stools	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Abdominal cramps	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Muscle or joint pain	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Fatigue/exhaustion	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Headache	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
Difficulty concentrating	not at all	☐	☐	☐	☐	☐	☐	☐	
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	(0-28) ___ ___
									Total MAS (0-252) ___ ___ ___

Eidesstattliche Versicherung

„Ich, Benno Sander, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Validierung und kritische Evaluierung des Mastozytose Aktivitätsscore“ bzw. „Validation and Critical Evaluation of the Mastocytosis Activity Score“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.org) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an etwaigen erfolgten Publikationen

Herr Benno Sander, geboren in Bonn, hatte Anteil an der folgenden Publikation:

Siebenhaar F, Sander B, Tram H, Ellrich A, Maurer M, Weller K. Development and validation of the mastocytosis activity score. Allergy. 2018;73:1489–1496. https://doi.org/10.1111/all.13425

Beitrag im Einzelnen:

Bei der von Herrn Sander in Koautorenschaft erstellten Publikation handelt es sich um eine Arbeit aus der Dermatologie, in der medizinische und statistische Fachkenntnisse verbunden wurden. Im Rahmen der veröffentlichten Studie wurde das Patient Reported Outcome Instrument „Mastocytosis Activity Score (MAS)“ auf Deutsch und Englisch entwickelt und auf Validität, Reliabilität und mögliche externe Einflussfaktoren, geprüft. Ein valides und reliables, Mastozytose-spezifisches Patient Reported Outcome Instrument hat das Potential Therapie und klinische Forschung der Mastozytose erheblich zu verbessern und sie nach aktuellen Standards der Federal Drug Administration und der Europäischen Arzneimittelagentur weiterhin durchzuführen.
Die Studie wurde von PD Dr. med. Frank Siebenhaar konzipiert. Ab Planung der Validierung des MAS wurde Herr Sander miteingebunden.
Im Rahmen der Validierung des MAS führte Herr Sander folgenden Aufgaben durch:

- Rekrutierung der StudienpatientInnen mit Durchführung von Erstgesprächen zur Diagnosesicherung sowie zur Studienaufklärung.
- Strukturierung und Koordination der MAS Fragebögen und Entsendung an PatientInnen.
- Instruktion der PatientInnen zum Ausfüllen der die Studie begleitenden Fragebögen (MC-QoL, SF-12, PGA disease severity, PGA quality of life).
- Erstellung der Studiendatenbank und Dateneingabe in IBM SPSS Statistics Version 22, IBM Corporation, Armonk, NY, USA.
- Mitbestimmung der Ausschlusskriterien für die Studie.
- Mitbestimmung der angewandten Testverfahren zur Messung der Validität.
- Analyse der Testergebnisse und Bestimmung der finalen MAS Struktur.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

Unterschrift des Doktoranden

Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

Siebenhaar F, Sander B, Tram H, Ellrich A, Maurer M, Weller K. Development and validation of the mastocytosis activity score. Allergy. 2018;73:1489–1496. https://doi.org/10.1111/all.13425

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Mein Dank gebührt:

Meinen Eltern, stets mit einem offenen Ohr und einem aufmunternden Wort zur Seite.

Frank Siebenhaar, für seine stoische Geduld und Unterstützung.