

Developing symptom lists for people with cancer treated with targeted therapies

Running heading: Targeted Therapy Symptom Lists

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Consent to Participate

Ethical approval for this study was awarded for the Lead site (NRES Committee South Central Southampton B 11/SC/0412). Each collaborating centre also received their local approvals. All participants gave their informed consent to participate and for their anonymous data to be shared.

Consent for Publication

All authors and the EORTC QLG granted their permission for the publication of this manuscript.

Availability of data and material

Raw data generated from this work cannot be shared as permissions were not requested from participants. The symptom set generated from this work is available from the EORTC QLG upon request <https://qol.eortc.org/questionnaires/>

Code availability

Not applicable

Authors Contributions

All authors contributed to the manuscript preparation, editing and review.

Abstract

Background

Targeted therapies (TTs) have revolutionised cancer treatment with their enhanced specificity of action. Compared with conventional therapies, TTs are delivered over a longer period and often have unusual symptom profiles. Patient reported outcome measures such as symptom side-effect lists need to be developed in a time-efficient manner to enable a rapid and full evaluation of new treatments and effective clinical management

Objective

The aim of this study is to develop a set of TT-related symptoms and identify the optimal method for developing symptom lists.

Patients and Methods

Symptoms from TT treatment in the context of Chronic Myeloid Leukaemia (CML), HER2 positive breast cancer, or Gastrointestinal Stromal Tumours (GIST) were identified through literature reviews, interviews with health care professionals (HCPs) and patients, and patient focus groups. The symptom set was then pilot tested in patients across the three cancer diagnoses: The number of items derived from each source (literature, patients, or HCPs) were compared.

Results

A total of 316 patients and 86 HCPs from 16 countries participated. An initial set of 209 symptoms was reduced to 61 covering 12 symptom categories. Patient interviews made the greatest contribution to the item set.

Conclusions

Symptom lists should be created based on input from patients. The item set described will be applicable to the assessment of new TTs, and in monitoring treatment.

Key Points

Development of symptom measures needs to be rapid to respond to the ever-changing treatment landscape.

Symptom sets are a resource to create symptom lists in a time-efficient manner.

The content of symptom lists should be informed by patient experience.

1. Introduction

Patient reported outcome (PRO) measures provide an assessment of a patient's health condition from the patient's perspective rather than relying on the interpretation of others, such as clinicians (1). In recent years there has been increased focus on PROs in clinical trials, clinical practice, and health technology assessments (2-5). The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend the use of PRO measures in marketing applications for new treatments (2, 4) and place emphasis on patient-reported symptoms. Symptom assessment enhances precision in describing the patient's symptom experience as well as monitoring treatment side-effect profiles (6). Online symptom reporting by patients with cancer can facilitate comprehensive symptom capture in real time, reduce costs and allow for timely detection and

management of symptoms (7-9). This can translate into improved patient experience and outcome (10). The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) enables patients to report symptoms related to cancer and its treatment directly onto a trial database (11). Others have used a more flexible computer-adaptive testing approach to tailor symptom assessment according to patient relevance, and thus reduce respondent burden (12, 13). All these systems require the identification and/or construction of many items which can be labour-intensive and costly.

Cancer- and treatment-related symptoms have a significant impact on health-related quality of life (HRQOL) and form an integral part of its definition and assessment. Symptom items feature strongly in HRQOL assessments. For example, 17 of 30 items in the widely used EORTC Quality of Life core cancer questionnaire, the EORTC QLQ-C30, refer to symptoms. However, symptom lists alone do not provide a full assessment of HRQOL, which includes the broader domains of physical, role, cognitive, emotional, and social functioning (14).

Targeted therapies (TTs) have revolutionised treatments of several cancers especially HER2 positive breast cancer (trastuzumab) (15), haematological malignancy such as Chronic Myeloid Leukaemia (CML) (16), and Gastro Intestinal Stromal Tumours (GISTs) (imatinib) (17, 18), by substantially improving clinical outcomes since their approval towards the end of the last century and the early 2000s. TTs selectively target molecular agents involved in tumour growth and progression. Despite their selectivity, TTs cause a range of unexpected and unpredictable symptoms, such as rash and headache, rarely seen with traditional treatment. In our review of the literature on the side-effects of TTs used for GISTs, skin-related problems, particularly Hand-Foot syndrome associated with sunitinib, were reported in nearly half of the papers reviewed affecting 37% of patients in the randomised clinical trials and case reports reviewed (19). Furthermore, TTs are delivered for much

longer than standard chemotherapy, with a longer exposure to potential side-effects. With long-term drug administration, low-grade side-effects may significantly interfere with patients' wellbeing and daily functioning and may be overlooked (20, 21). These unusual symptoms are likely to go undetected by HRQOL questionnaires developed before the widespread use of TTs.

In addition to the EORTC Quality of Life core cancer questionnaire, the EORTC Quality of Life Group (QLG) has developed a suite of questionnaires specific to different tumour or condition types using a rigorous and time-consuming process (22). A more flexible and dynamic approach has been proposed which recognises the need to keep pace with the ever-changing treatment landscape and includes symptom side-effect questions as an add-on to EORTC measures. (6). This strategy is facilitated by the EORTC QLG Item Library which includes nearly 1000 validated, multi-lingual items from the EORTC questionnaires (23, 24). Recent studies adopting this flexible approach include routine electronic monitoring of HRQOL in metastatic renal cell cancer, which used the EORTC QLQ-C30 with nine questions from the Item Library to assess common treatment-related symptoms (25) and a study of rare cancers in which 10 items were selected from the Item Library to supplement the EORTC QLQ-C30 (26).

The aim of the current study was to identify a symptom set for patients treated with TTs using the EORTC QLG Module Guidelines (22) and to use this process to inform recommendations for the optimal method for developing symptom lists across different patient groups.

2. Methods

The development process covered three phases: Phase 1: identification of symptoms to include in the item set, from systematic reviews of the literature, interviews with patients and health care professionals (HCPs) with experience of TTs and patient focus groups; Phase 2: selection of symptoms and creation of the item set; Phase 3: Pilot testing the item set in patients to ensure

acceptability, comprehension and completeness of the set. Interviews were conducted in several countries and languages to ensure multi-cultural relevance.

2.1 Tumour types and targeted therapies

We recruited patients treated (either currently or previously) with TT for either CML, HER2 positive breast cancer, or GIST, cancer types in which TTs featured prominently within their treatment at the time of writing the protocol for this study. Given that different TTs are used to treat these cancers, it was anticipated that we would capture a broad range of symptoms. In addition, these cancer scenarios were chosen for pragmatic reasons with each one having a different starting point for the generation of the item set, explained below.

CML is a common haematological malignancy and TTs are now widely used in its treatment. Indeed, these therapies have remarkably improved survival of patients with CML (27). When the present study began, there was an EORTC CML-specific questionnaire in development (EORTC QLQ-CML24) (28). We therefore used the symptom data collected as part of that work (28) to inform the development of the item set.

Breast cancer is a common cancer, and was one of the first to benefit from TTs with the introduction of trastuzumab (29, 30). The development of the EORTC breast cancer module (EORTC QLQ-BR23) (31) was completed in 1996 before the advent of TTs.

GIST is a rare cancer which also responds well to TTs. Historically, in the context of advanced or unresectable GISTs, treatment options were limited. TTs such as imatinib have become the standard therapy (31), There is currently no GIST-specific EORTC module to assess the impact of GIST and its treatment on HRQOL .

2.2 Scope of the Item Set

We adapted a dictionary definition of symptoms for the purpose of this study (32). Symptoms eligible for inclusion in the item set were defined as those described by patients as a “**physical or**

psychological disturbance from normal biological function, sensation or appearance (but not the impact or interference with normal activities arising from such disturbances, such as activity limitations, or body image)". In this study our focus was on symptoms **which are a consequence of treatment**, rather than a marker of the disease itself, although we acknowledge that the distinction between treatment-related and disease-related symptoms is not always clearly delineated. Medically defined changes such as abnormal blood tests or a diagnosis based on clinical investigation rather than patient experience were excluded.

Although only the three disease scenarios mentioned above were included in the development of the item set, the intention was for the item set to be used and adapted for different cancer and TT types.

2.3 Phase 1

2.3.1 Literature reviews

Systematic reviews of the literature relating to toxicities of TTs for CML, breast cancer, and GIST have been reported elsewhere (19, 33, 34).

2.3.2 Patient interviews and focus groups

In the development of the QLQ-CML24, patients with CML were interviewed and asked to rate the relevance and importance of HRQOL concerns (including symptom issues) captured from the literature. Full details are reported elsewhere (28).

Interviews were conducted with patients diagnosed with HER2 positive breast cancer or GIST. The numbers of patients interviewed were in accordance with QLG Guidelines (22). Patients who were receiving or had previously received TT for breast cancer or GIST were invited to participate by their clinician. In addition, patients with GIST were recruited for telephone interviews through the GIST UK Support Group website. Finally, a focus group was conducted for each diagnosis in Southampton,

UK. The focus groups provided an opportunity for patients to collectively review the set of symptoms captured thus far and to consider new symptoms.

In a semi-structured interview, or focus group, patients were asked to consider their experiences while taking TT and to only report, where possible, side-effects they associated with TTs, rather than the cancer itself, other treatments, or other factors such as pre-existing conditions and age.

The interview and focus group schedules are presented as supplementary material (Supplementary material 1).

2.3.3 HCP Interviews

As part of the development of the EORTC QLQ-CML24, interviews were conducted with HCPs who treat CML (28).

Interviews with HCPs, with specialist experience in breast cancer or GIST were also carried out at each participating centre. The interviews were carried out in parallel with the patient interviews. HCPs were asked to report side-effects they associated with TTs.

2.4 Phase 2

2.4.1 Selection of symptoms

The researchers reviewed all symptoms generated from the interviews, focus groups and literature reviews. Symptoms generated by more than one data capture method (literature, interviews (patients and HCPs) or focus groups), and those with a prevalence of at least 5% of interviews were considered for retention. Symptoms with closely related content were rejected or combined to avoid redundancy.

2.4.2 Item generation

Questions included in existing EORTC quality of life questionnaires were firstly reviewed to identify whether they offered a good match to the symptoms identified. The wording of existing EORTC questions was sometimes adapted to adequately cover the symptom under consideration. When

there was no corresponding item, new symptom questions were constructed. A time frame of “the last week” for recall of symptoms was chosen, for consistency with the usual time frame of validated EORTC items although, for some symptoms, where little change would be expected over a week, the time frame of “the past 4 weeks” was adopted .

2.4.3 Clinical review and translation

The item set for breast and GIST patients was sent to six health professionals in the participating centres. Reviewers were asked to consider whether the items were relevant and appropriate for their patients and to consider any important omissions. The CML items also underwent clinical review and translation as part of the development of the EORTC QLQ-CML24.

2.5 Phase 3: Pilot testing the item set

A draft item set was pilot tested with a separate group of patients diagnosed with CML, breast cancer, or GIST, and who were receiving or had previously been treated with TT. Patients were asked to complete the EORTC QLQ-C30 and the draft item set, and to rate the incidence, relevance and importance of each symptom from “not at all” to “very much”. They were also asked to identify any important omissions from the set and whether any items were upsetting or inappropriate, or difficult to understand. Items reported as confusing, and those displaying overlap with other items were considered for rejection.

2.5.1 Generation of recommendations for developing item sets

In order to evaluate the contribution of each method of symptom capture (literature, patients and HCPs) to the provisional and final item set, the number of symptoms captured by each method was compared. This comparison informed recommendations for the optimal practice of generating symptom lists.

2.5.2 Ethics

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved at the lead site (University of Southampton, United Kingdom) by NRES Committee South Central Southampton B (11/SC/0412). All patients gave informed written consent to participate.

3 Results

3.1 Phase 1

3.1.1 Literature reviews

Of the 74 HRQOL issues identified from the CML literature review (34), 45 described symptoms. Forty-one issues were identified from the physical symptom category list (such as swelling, cramps and gastro-intestinal symptoms) and four from the psychosocial category (such as depression and worry).

The breast cancer literature review identified a total of 46 symptoms (33). Diarrhoea and skin rash were the most prevalent symptoms, experienced by 29% and 22% of patients overall. Most symptoms (n = 52) were experienced by 1% or less of patients and were predominantly of Grade 1/2 toxicity.

Our review (19) of symptoms experienced during treatment with TTs for GIST identified 64 symptoms covering physical side-effects such as fatigue, nausea, and oedema, as well as psychological symptoms of depression, confusion and concentration problems. Fifty-six (88%) symptoms were captured from studies reporting side-effects of imatinib and 33 (52%) related to sunitinib. Important differences in the symptom profiles of imatinib and sunitinib were seen in the frequencies of oedema, muscle and joint pains, skin and oral conditions.

3.1.2 Interviews and focus groups

3.1.2.1 Patients

Interviews were conducted with 137 patients receiving treatment for CML (mean age of 56.7 years) in seven hospitals in Germany, Greece, Italy, Iraq and Taiwan (28). Forty-three percent of patients were on treatment with first line imatinib and 46% were on second-line treatment with second generation TKIs (nilotinib and then dasatinib). About half of the patients (53%) had been treated for more than five years. An additional 99 patients were recruited through an Italian CML patient advocacy website and invited to comment on the HRQOL issues. Data generated from this sample were used for supportive analysis.

Fifty-three female patients with breast cancer, 47 of whom were currently receiving TT (s) were interviewed across five countries and an additional 5 patients attended a focus group (Table 1).

Twenty-seven patients from three countries currently on TT for a GIST were interviewed and a further 5 patients attended a focus group (Table 1).

Table 2 outlines the clinical characteristics (including type of TT) of the patients with breast cancer and GIST.

3.1.2.2 Health Care Professionals

Fifty-nine HCPS from 12 countries treating patients with CML were interviewed as part of the EORTC QLQ-CML24 development (28). Twenty-five HCPs with expertise in treating breast cancer or GIST were also interviewed (Table 3).

3.1.3 Symptoms

Forty-five CML-related symptoms were identified in the development of the EORTC QLQ-CML24; 112 symptoms were reported by patients with breast cancer, and 141 by those with GIST.

In the HCP interviews, a total of 72 symptoms were identified for breast cancer and 53 symptoms were identified for GIST.

Patients described 209 symptoms (Table 4). Of these, 61 were reported within the context of breast cancer, 77 in GIST and 70 in both tumour types. One additional symptom (problems with sweating) was obtained from the CML data (Table 5).

3.1.4 Contribution of each method to the development of the item list

Forty-seven symptoms in the draft list were captured by all sources (literature, patients and HCPs). Each source of symptoms gave some unique issues (Table 4) with patients offering the greatest contribution of these: the literature and HCPs identified one unique symptom each (Infections was uniquely captured in the literature and bleeding gums mentioned only by HCPs) while patient interviews identified six unique symptoms (frequent urination, feeling tense, heart palpitations, pale/cold fingers, impaired motivation and sensitivity of the skin to the sun). In addition to infections and bleeding gums, only two other symptoms (painful bowel movements and cough) were not mentioned by patients.

3.2 Phase 2

3.2.1 Selection of symptoms

Figure 1 outlines the process of reduction of symptoms into the draft item set. This included 74 symptoms, organised in 15 categories (Table 4). With the exception of infection, weight gain and weight loss, which were rated “during the past 4 weeks”, all symptoms were scored “during the past week”.

3.3 Phase 3

3.3.1 Pilot testing the draft item set

One hundred and two patients from seven countries completed the draft item set (Supplementary material 2; Table 2.1). Just over half the sample (51%) had breast cancer, followed by GIST (34%) and CML (15%). Patients had experience of treatment with at least one of 10 TTs (Supplementary material 2; Table 2.2), the most common TT was imatinib (41%) followed by trastuzumab (38%), and

32% started TT in the last 6 months. Except for two patients, all respondents were currently receiving treatment.

The prevalence of symptoms across all three cancer types and different TTs was low. For 29 symptoms, fewer than 10% patients rated their severity “quite a bit” or “very much”. The two most frequently reported symptoms were lack of energy (45%) and tiredness (42%). These symptoms were recognised as relevant and important by over two-thirds of patients (68% and 69% respectively).

After a review of patient comments, 13 items were removed, and some adjustments were made to the categories (Table 4). No new symptoms were identified. The remaining 61 items are presented in Table 5 with the disease scenario in which they were reported during Phase 1 interviews, focus groups and literature reviews. Table 5 shows the distribution of symptoms across cancer types; some symptoms were unique to one cancer, for example, heart palpitations and breast cancer (trastuzumab) and red (bloodshot) eyes and GIST (imatinib). The symptoms are organised within categories for convenience, but this does not imply that there is a scale structure.

Eight symptoms (skin rash, sore or painful skin, palpitations, dry eyes, itchy eyes, nose bleeds, other nose problems, dizziness) were not identified within the EORTC QLG Item Library and represent new items and 15 (e.g., skin colour changes, itchy skin, watery eyes) required adaptations of existing EORTC QLG items.

3.3.2 Contribution of each method to the development of the final item set

Patients made the greatest contribution to the final symptom set with 58 of the 61 symptoms mentioned by patients during Phase 1 interviews and focus groups, compared with 47 presented by HCPs and 52 symptoms identified in the literature.

4. Discussion

This paper describes the process of identifying and creating a set of symptoms experienced by patients with three different cancers treated with a range of TTs. The well-established QLG methods (22) for item generation were used. Comparison of the source(s) of each item has enabled the formulation of recommendations for developing and using item lists for specific TTs and tumour sites.

4.1 Creating Item Lists

In line with the robust EORTC QLG recommendations for questionnaire generation (22), three sources were used to identify potential symptoms for inclusion in the item set and we were able to compare the input from each source. Data were retrieved from interviews with patients and HCPs, patient focus groups and systematic reviews of the literature. Literature reviews were time-consuming and labour-intensive. None of the symptoms identified *only* from the literature reviews were included in the final item set. To identify side-effects of new treatments during development, a full systematic review is unlikely to be productive.

Patients' accounts of symptoms offered the greatest contribution to the content of the item set and we therefore recommend, as a minimum, involving patients in the development of symptom lists. Our recommendation to prioritise patient interviews in the development of symptom lists will ensure content validity as well as reduce the resource burden on the development process. This mirrors other work underlining the importance of the patient's voice in the identification of symptoms to be included in PRO measures (26).

During product development, patient experience with a new drug may be limited. The greatest amount of patient-reported data on symptoms associated with a new treatment is likely to be in the case report forms from phase 1 and 2 clinical trials. We recommend consulting these data when an item list is created to be used in a phase 3 clinical trial.

The EORTC QLQ Item Library is a valuable resource when creating item lists (23). It consists of items that have been developed with care to avoid confusing phrasing, and to facilitate translation; the items have all been widely tested and found to be acceptable in a variety of cultures, and all items have already been translated into many languages. Most items (87%) included in our item set were obtained from the EORTC QLQ Item Library, although a small number required slight modification. For eight symptoms not covered by existing items, new questions were developed using a format consistent with existing items. These have now been added to the Item Library. All items included in the set, including the newly created ones, were acceptable to patients during pilot testing which suggests that this method could be replicated for other conditions or treatments. These items will make a valuable contribution to the rapid development of measures to evaluate new treatments across different tumour types, consistent with EORTC QLQ strategy (5). The EORTC QLQ is currently developing guidelines to assist researchers design new, perhaps trial-specific, symptom questionnaires, during development of new therapies. The symptoms set may also be used to monitor treatment with TTs, for example to document the response to changes in therapy.

4.2 Recommendations for optimising practice for generating item lists

The following recommendations for developing an item set are proposed:

1. Identify relevant issues using patient interviews in the target population.
2. Supplement the interview data with a review of clinical reports and preclinical trial data.
3. Search the EORTC QLQ Item Library for relevant questions. If new items are required, EORTC QLQ guidance should be followed.

4.3 Using Item Lists

Current EORTC QLQ strategy recommends using additional items from the EORTC QLQ Item Library as an “add-on” to supplement the EORTC QLQ-C30 and existing disease-specific measures. This

strategy aims to enhance sensitivity to the side-effects of new treatments (23, 24) and should facilitate the measurement of adverse events of new treatments, and their impact on the common functional health problems reported by patients.

In the context of two of the cancer types investigated in the current study, CML and breast cancer, an item list could be used alongside the EORTC QLQ-C30 and the relevant disease-specific module. In breast cancer, for example, a clinician or researcher could use the EORTC QLQ-C30 with the newly-updated EORTC QLQ-BR45 (35), and add the symptom items of broken nails and heart palpitations. For GIST, where there is currently no specific module, an item set could be used to record swelling, cramps, eye and skin problems, to complement the EORTC QLQ-C30, with the caveat that the item set provides data only about treatment-related symptoms rather than GIST-specific functioning.

In some cases, an investigator may be concerned with comparing specific symptoms associated with different treatments, rather than the full symptom profile. The symptom set generated in this study is organised into categories to facilitate the generation of focussed symptom lists, for example, to assess gastro-intestinal or skin symptoms.

Item lists could serve as a valuable tool to support clinicians' consultations with patients, enhancing the quality and content of such consultations (36). A set of questions about symptoms could be completed before the patient sees the clinician. This will identify symptoms relevant to the patient to be discussed during the consultation, supporting the delivery of personalised care. Showing patients symptom lists prior to their consultation could open up conversations about rare and unexpected symptoms which might otherwise be overlooked and might serve as an early warning system. Some of the symptoms (e.g., skin colour changes) in the list we generated were not mentioned by HCPs perhaps because untreated, they are not likely to have serious health implications. However, these symptoms can affect patients' HRQOL and compliance with treatment. HCPs are unlikely to have treatments to overcome these symptoms, yet they remain very relevant to patients. Having this information about a list of symptoms that patients believe to be relevant to

their well-being is critical to open consultations that meet a patient's needs and could inform the development of symptom control treatments.

4.4 Caveats

The item set presented is not intended for use in its entirety; not all symptoms are relevant for all disease and treatment scenarios.

Although the item set generated in this study is extensive in its coverage of symptoms, the set is expected to expand to accommodate novel symptoms reported by patients treated with new and different TTs.

It is important to reiterate that item lists do not provide a comprehensive measure of HRQOL. Rather they can supplement existing HRQOL measures.

We do not recommend generating a total score from item lists; each item should be scored separately rather than used to create sub-scale scores.

4.5 Strengths of the study

This study used the rigorous methodology of the EORTC QLG (22) which involved different strategies of generating symptoms related to a variety of TTs used in the treatment of three different cancer types. This ensured comprehensive coverage of potential items, and multinational, multilingual development. The study design also lent itself to a comparison of the unique contribution of each method of symptom-capture: literature, patients and HCPs.

4.6 Limitations of the study

This study developed an item set that would be useful for symptom reporting by patients receiving TTs. For practical considerations the patient groups were limited to three tumour types, and the therapies included were those in wide use at the time of the study. Additional symptoms may be

experienced with other tumours or new therapies. However, we have offered recommendations for the creation of bespoke symptom lists specific to other TT types. Although at the outset we defined the scope of what would be considered a symptom, some issues initially selected for inclusion were subsequently rejected as they did not fit the symptom definition, suggesting that there was initial lack of clarity in the application of the symptom definition. Finally, symptoms were only selected if they were perceived by the patient as specifically TT-induced. The challenge of identifying symptoms that are exclusively treatment-related is widely acknowledged (37) and we relied on patient recall of onset, and whether dose modification led to an improvement in symptoms. We aimed to be inclusive of symptoms rather than rigorous in attributing their cause.

5. Conclusion

This study has demonstrated the feasibility of developing a patient-reported assessment of symptoms specific to novel TTs using the robust methods recommended by the EORTC QLG. Our study underlines the central role of patients in the development of PRO measures including item sets. We recommend that investigators and clinicians can select individual symptoms from the Item Library to create bespoke symptom assessments to supplement HRQOL assessment. Such a list would include symptoms expected to change with a treatment, or symptoms which require careful monitoring and management.

Table 1. Demographic characteristics of GIST and breast cancer patients

	Breast cancer Interviews (N=53)	Breast cancer Focus Group (N=5)	GIST Interviews (N=27)	GIST Focus Group (N=5)
Patients per country N(%)				
UK	13 (25%)	5 (100%)	19 (70%)	5 (100%)
Poland	7 (13%)	0	5 (19%)	0
Cyprus	15 (28%)	0	3 (11%)	0
France	13 (25%)	0	0	0
Greece	5 (9%)	0	0	0
Gender				
Female	53 (100%)	5 (100%)	13 (48%)	2 (40%)
Male	0	0	14 (52%)	3 (60%)
Age (years)				
mean (SD)	56.15 (10.66)	50.80 (9.86)	58.4 (15.4)	52.6 (6.4)
range	32-82	38-64	20-85	44-62
Education level				
Less than compulsory	2 (4%)	0	0	0
Compulsory school education	13 (25%)	3 (60%)	10 (37%)	3 (60%)
Post compulsory school education (college)	22 (42%)	0	5 (19%)	1 (20%)
University	16 (30%)	1 (20%)	12 (44%)	1 (20%)
Unknown	0	1 (20%)		
Employment status				
Full time	12 (23%)	0	5 (19%)	2 (40%)
Part time	7 (13%)	1 (20%)	4 (15%)	1 (20%)
Homemaker	8 (15%)	1 (20%)	1 (4%)	0
Retired	14 (26%)	1 (20%)	15 (56%)	1 (20%)
Other ¹	12 (23%)	2 (40%)	2 (7%)	1 (20%)
Living situation				
Alone	4 (8%)	1 (20%)	2 (7%)	1 (20%)
Partner	25 (47%)	4 (80%)	16 (59%)	2 (40%)
Others	24 (45%)	0	9 (33%)	2 (40%)

¹Other employment categories included sick leave, unemployed, and semi-retired

Table 2 Clinical characteristics of GIST and breast cancer patients

	Breast cancer Interviews (N=53)	Breast cancer Focus Group (N=5)	GIST Interviews (N=27)	GIST Focus Group (N=5)
Disease status				
Localised	32 (60%)	0	10 (37%)	2 (40%)
Metastatic	20 (38%)	5 (100%)	17 (63%)	3 (60%)
Missing	1 (2%)	0	0	0
Years since initial diagnosis				
<5	41 (77%)	3 (60%)	14 (52%)	3 (60%)
5-10	8 (15%)	0	10 (37%)	2 (40%)
10-15	3 (6%)	2 (40%)	2 (7%)	0
>15	1 (2%)	0	1 (4%)	0
Treatment				
Trastuzumab	45 (85%)	5 (100%)		
Bevacizumab	7 (13%)	1 (20%)		
Trastuzumab and Pertuzumab	1 (2%)	0		
Imatinib			27 (100%)	5 (100%)
Sunitinib			9 (33%)	0
Regorafenib			5 (19%)	0
Co-morbidities				
None	42 (79%)	5 (100%)	17 (63%)	2 (40%)
Renal	0	0	0	1 (20%)
Cardiac	5 (9%)	0	2 (7%)	0
Respiratory	1 (2%)	0	1 (4%)	0
Rheumatic	1 (2%)	0	3 (11%)	0
Diabetes	1 (2%)	0	0	0
Other ¹	6 (11%)	0	4 (15%)	2 (40%)
ECOG Performance Status				
0	39 (74%)	3 (60%)	20 (74%)	4 (80%)
1	13 (24%)	1 (20%)	4 (15%)	1 (20%)
2	1 (2%)	1 (20%)	2 (7%)	2 (40%)
Missing	0	0	1 (4%)	0

¹Other co-morbidities include thyroid problems, hypertension, hip replacement, chronic fatigue syndrome, Parkinson's, depression, eye problems, Miller-Fisher Syndrome, skin problems, lupus and myasthenia.

Table 3. Recruiting country and specialist discipline of the Breast cancer and GIST HCPs*

	Breast cancer (N=16)	GIST (N=9)
HCPs per country	N(%)	N(%)
UK	6 (38%)	6 (67%)
France	4 (25%)	0
Poland	4 (25%)	0
Cyprus	0	3 (33%)
Greece	2 (13%)	0
Specialist discipline		
Medical / Clinical Oncology	13 (81%)	6 (67%)
Nursing	3 (19%)	2 (22%)
Palliative Medicine	0	1 (11%)

*HCP: Health care professionals

Table 4. Number of items across the symptom categories in the draft and final item set, and contribution made by each method to the item sets

Symptom Category	Draft	Final	Comment	Symptoms not captured by all methods
Skin	8	6	2 redundant items (sores/ulcers and sun sensitivity) removed	<ul style="list-style-type: none"> • Colour change (literature and patients only); • Sores/ulcers (patients and HCPs only) • Sun sensitivity (patients only)
Swelling	2	2		Captured by all methods
Musculo-skeletal	4	4		<ul style="list-style-type: none"> • Bone pain (patients and HCPs only) • Back pain (literature and patients only)
Mouth	5	5		<ul style="list-style-type: none"> • Bleeding gums (HCPs only)
Nails (and hair)	1 (and 3)	1	Hair items omitted because long term changes, and difficult to attribute	Captured by all methods
Heart and breathing	4	4	Categories combined; two items in each	<ul style="list-style-type: none"> • Heart palpitations (patients only) • Chest pain (literature and HCPs only)
Fatigue/energy	3	3		Captured by all methods
Eyes	7	7		<ul style="list-style-type: none"> • Dry eyes (patients and HCPs only) • Itchy eyes (patients and HCPs only)
ENT	4	4		<ul style="list-style-type: none"> • Changes to voice (literature and patients only)
Emotional function	5	5	Combined emotional (3 items) and cognitive (2 items) symptoms.	<ul style="list-style-type: none"> • Concentration (literature and patients only) • Tense (patients only) • Irritability (literature and patients only)
Digestion	13	11	Combined 3 groups: bowels, upper gastrointestinal tract, eating and appetite. 2 items redundant/not relevant including restricted diet and change in bowel habits	<ul style="list-style-type: none"> • Bowel urgency (patients and HCPs only) • Painful bowel movements (literature and HCPs only) • Flatulence (literature and patients only)

				<ul style="list-style-type: none"> • Indigestion (literature and patients only)
General	15	9	6 items not relevant or did not fit time frame (weight gain, weight loss, infections, frequent urination, fainting, feeling unwell)	<ul style="list-style-type: none"> • Hot flushes (patients and HCPs only) • Infections (literature only) • Pale/cold fingers and toes (patients only) • Tingling/numbness in hands or feet (literature and patients only) • Frequent urination (patients only) • Motivation (patients only)

Notes:

Musculo-skeletal refers to symptoms affecting the joints, bones and muscles.

ENT: symptoms arising in the ears, nose or throat

Table 5. Symptoms represented in the final item set and reported incidence according to cancer type

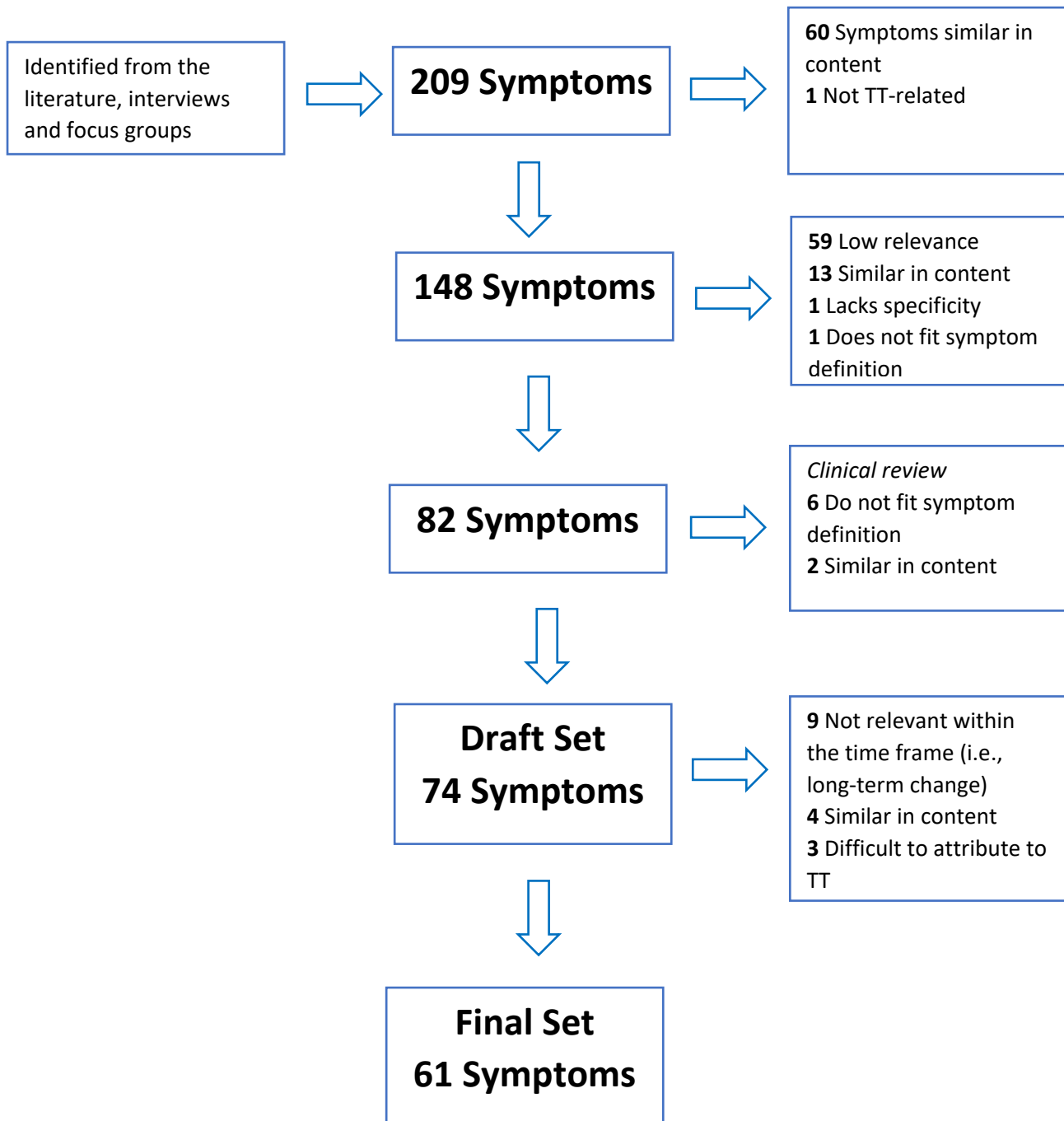
Symptom Category	Symptoms	CML	Breast cancer	GIST
Skin	Skin colour change	✓	✓	✓
	Itchy skin	✓	✓	✓
	Skin rash	✓	✓	✓
	Dry, flaking or cracked skin	✓	✓	✓
	Sore or painful skin	✓	✓	✓
	Bruises	✓	X	✓
Swelling	Swelling of legs and ankles	✓	✓	✓
	Swelling of face or around the eyes	✓	X	✓
Musculo-skeletal	Muscle aches, pains or cramps	✓	✓	✓
	Aches or pains in joints	✓	✓	✓
	Aches or pains in bones	X	✓	✓
	Back pain	X	✓	✓
Mouth	Dry mouth	✓	✓	✓
	Taste change	✓	✓	✓
	Pain or soreness in mouth	✓	✓	✓
	Bleeding gums	X	✓	X
Nails	Nails have broken easily	X	✓	X
Heart and breathing	Heart palpitations	X	✓	X
	Chest pain	✓	✓	✓
	Shortness of breath	✓	✓	✓
	Cough	X	✓	✓
Fatigue/ energy	Tiredness	✓	✓	✓
	Weakness	✓	✓	✓
	Lack of energy	✓	✓	✓
Eyes	Watery eyes	✓	✓	✓
	Dry eyes	X	✓	✓
	Red (bloodshot) eyes	X	X	✓
	Itchy eyes	X	✓	✓
	Burning eyes	✓	✓	✓
	Sensitivity of eyes to the light	✓	✓	X
	Blurred vision	✓	X	✓
ENT	Nose bleeds	X	✓	✓
	Other nose problems (smell, sneezing)	X	✓	✓
	Hearing problems	✓	✓	X
	Changes to voice	X	X	✓

	Sore throat	X	√	√
Emotional function	Depressed	√	√	√
	Tense	X	√	X
	Irritable	√	√	√
	Memory problems	√	√	√
	Concentration	√	√	√
Digestion	Diarrhoea	√	√	√
	Constipation	√	√	√
	Toilet urgency	X	X	√
	Painful bowel movements	X	√	√
	Flatulence	X	√	√
	Indigestion (heartburn)	√	√	√
	Nausea	√	√	√
	Vomiting	X	√	√
	Appetite loss	√	√	√
	Abdominal pains and cramps	√	√	√
	Abdominal bloating	X	√	√
General	Fevers or chills	√	√	√
	Hot flushes	X	√	√
	Excessive sweating	√	X	X
	Headaches	√	√	√
	Tingling or numbness in hands or feet	X	√	√
	Pale or cold fingers or toes	X	√	√
	Feeling unwell	X	√	√
	Dizziness	√	√	√
	Trouble sleeping	√	√	√

Note. Symptoms are scored according to whether they had been experienced within the past week

√= present; X = absent

Figure 1. Process of selection of symptoms



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