Towards a patient-driven approach to adverse events of targeted agents in oncology

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08 | General discussion, summary & future perspectives

General discussion and summary

This thesis presents three notable findings: the voice of the patient is inconsequently incorporated in scientific research regarding AEs; available instruments may be of limited value for approaching targeted therapy-associated mucocutaneous AEs; and available knowledge about a patient-driven approach to AEs is not broadly incorporated in research and clinical care.

The voice of the patient is inconsequently incorporated in scientific research and the HCP plays the central role in AE diagnosis and management. The incidence of the AEs is mainly measured by HCP's with suboptimal scales. As a result there may be underreporting of AEs. In addition, the non-validated CTCAE scoring system for the grading of the AEs is most commonly used while more precise grading instruments are available. Currently, most AE grading is performed by HCP's rather than by patients.

The instruments evaluated in this thesis may be of limited value for the education, assessment, reporting, grading, and evaluation of targeted therapy-associated mucocutaneous AEs since:

- there is no consensus on AE terminology, and therefore the same AEs may be diagnosed and named differently
- the majority of the instruments currently used were not developed for the AEs associated with targeted therapies
- some instruments were developed specifically for subgroups of the targeted agents; EGFRI, mTORI, and TKI
- not all the known symptoms and signs of AEs are incorporated in current instruments
- the majority of the instruments are not validated, and
- the majority of the instruments are not available in multiple languages.

In addition, the number proven approaches for the treatment of skin and mucosal AEs is limited. Studies to date mainly report secondary outcomes of larger studies with other primary outcomes. Furthermore, the AE studies are based on inconsistent terminology and the AEs are assessed and graded with suboptimal scales. There is a lack of prospective studies investigating the terminology, symptoms and signs of AEs, their impact on health related HRQoL, the reporting of AE characteristics, grading the AEs, and management of AEs with scales specifically developed for targeted agents. Instruments for PRO and CRO are available, but they are not used consequently.

Current knowledge about a patient-driven approach including education, terming, assessing, reporting, grading, evaluating, and treating targeted therapy specific AEs is not imbedded broadly in research.(1) In the several manuscripts of this dissertation

one or more of these crucial steps is addressed. The instruments evaluated in this dissertation are listed in **box 1**.

Box 1. Evaluated instruments listed in alphabetical order

- **Bristol Stool Chart:** The Bristol Stool Chart focuses on variation in consistency of stool.(2) The stools are classified into seven types, with types 5 and 6 tending towards diarrhea but still loose or mushy stool and type 7 actually diarrhea, watery stool. Since according to the NCI-CTCAE definition only type 7, the watery stool, is diarrhea, the differences between the two types is important.
- **DERETT:** The Dermatological Reactions Targeted Therapy (DERETT) is a targeted therapy specific instrument with focus on the assessment of the mucocutaneous AEs and the influence of these AEs on HRQoL. DERETT is available in two versions, a symptom experience diary for patients (DERETT-P) and a symptoms & signs assessment instrument (DERETT-H) for HCPs. These instruments gather information such as area involved, severity and duration of the symptoms, products used to treat symptoms, effectiveness of the supportive care interventions, treatment adherence, and symptom-related distress.(3)
- **EA:** The Experimental Assessment (EA) is an oral assessment instrument that assesses a number of symptoms using Visual Analogue Scale (VAS) (0–10) including dysgeusia, dysphagia, odynophagia, and oral mucosal pain which are subjective parameters. The scale adds an objective measure of mucosal erythema and ulceration.(4) The EA may have utility in assessing TKI- and mTORI-induced oral AEs.
- **FACT-EGFRI-18:** The Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18 (FACT-EGFRI-18) is an 18-item Likert-scaled PRO questionnaire. It is arranged in three HRQoL domains: physical (7 items), social/emotional (6 items), and functional well-being (5 items).(5-7) The validation of the Dutch Version of the FACT-EGFRI-18 is part of the BeCet trial.
- **FACT-G:** The Functional Assessment of Cancer Therapy-General (FACT-G) is a cancer specific instrument with focus on PRO measures using numerical analogue scales (0=not at all, 4=very much). The FACT-G version 4 consists of 27 items in four HRQoL domains: physical (7 items), social/family (7 items), emotional (6 items), and functional well-being (7 items).(8)
- **FAST-EGFRI:** The Functional Assessment of Side-Effects to Therapy-EGFRI (FAST-EGFRI) is an EGFRI specific instrument with focus upon the assessment of HRQoL.(7) The 38-item FAST-EGFRI was the first EGFRI specific HRQoL questionnaire.
- **MESTT**: The MASCC EGFR Inhibitor Skin Toxicity Tool© (MESTT) is a grading system for the most common EGFRI-associated mucocutaneous AEs.(9) The MESTT is an event-specific grading system that can be used to standardize assessment, optimize the use of EGFRIs, and enable researchers to conduct more

informative, controlled studies in this patient population. The scale is consistent with grading principles and language of the CTCAEv4.0.

- **mIAS scale:** The mammalian target of rapamycin inhibitor (mTORI)-associated stomatitis (mIAS) scale is a mTORI specific instrument with focus on mIAS.(10) This scale has a subjective component measuring pain and an objective component measuring duration of lesions.
- **MOATT**: The MASCC Oral Agent Teaching Tool© (MOATT) was developed to meet an identified need for HCPs involved in the education of patients receiving oral anticancer agents. The MOATT provides a structured format to ensure that all key areas of patient assessment and teaching are addressed. It allows for individualized teaching and uses evidence-based tenets in patient education. The MOATT is well researched and easy to use.(11)
- **NCI-CTCAE:** The National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE) is a general instrument used by clinicians to report toxic effects of cancer treatment. Currently, decisions about dose modifications due to AEs are based on clinician assessment utilizing the CTCAE grading system. Despite its widespread use and its utility, the CTCAE has not been validated.(12)
- **NCI-PRO-CTCAE**: The National Cancer Institute's Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) system provides a web-based platform to collect patient reports of symptoms for the purpose of enhancing AE reporting and grading.(12, 13)
- **OMAS:** the Oral Mucositis Assessment Scale (OMAS) focuses on objective measure of mucosal ulceration and erythema.(14)
- **Oral Care Protocol** is a generic education instrument with focus on oral hygiene.(15)
- **SF-36:** The 36-Item Short Form Health Survey (SF-36) focuses upon the measurement of functional status in general and specific populations, including oncology.(16) The questionnaire covers eight scales: physical functioning, role limitations due to physical health and due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health.
- **SKINDEX-16:** The Skindex-16 is a PRO assessing dermatological symptoms for general skin diseases using a numerical analogue scale. It contains three domains: symptoms (4 items), emotions (7 items), and functioning (5 items). It has been used to assess HRQoL in patients receiving EGFRI, but does not address symptoms related to hair, nails, or mucous membranes, that are specific targets for EGFRIs.(17)
- **VHNSS2.0:** The Vanderbilt Head and Neck Symptom Survey (VHNSS) version 2.0 was designed to screen both for tumor and treatment-related symptoms in patients with head and neck cancer undergoing concurrent chemoradiation. It assesses patient-reported symptom burden in the head and neck area and function loss within symptom subscales, including nutrition, taste, pain, voice, swallow, and mucous/dry mouth.(18, 19) The **modified VHNSS2.0** is adapted from the original

VHNSS2.0 to make it suitable for the targeted therapy population and is being tested in the COMTT trial.(3)

- **WHO OTS:** The World Health Organization (WHO) Oral Toxicity Scale (OTS) classification of oral toxicity that combines descriptions of mucosal changes, pain, and functionality into a single composite score(20, 21) that is mainly driven by the patient's ability to eat and drink.

In **chapter 2** the terminology of TKI and mTORI-associated oral AEs, assessment of symptoms and signs, grading and treatment of the AEs as one entity were addressed. The objective of this study was to provide an overview of the prevalence and characteristics of oral AEs with TKI and mTORI treatment and the current oral assessment instruments commonly used in clinical trials. It was discussed how these novel AEs can be assessed because current mucositis instruments have limitations for this patient population. Also explored were the correlations between oral AEs and HFSR and rash.

No consensus on AE terminology was found. This finding is consistent with the findings in the literature. The terminology and classification of oral AEs associated with targeted therapies has been inconsistent throughout different clinical trials. This makes comparison of AE data difficult. In the literature, the terms mucositis and stomatitis are used interchangeably, however, they do not reflect the same clinical condition.(12, 22) 'Stomatitis' refers more generally to any inflammatory condition of oral tissues,(12) but has been recommended for use in oncology in lesions with aphthous-like appearance such as oral lesions associated with targeted therapies. In a review article on the AEs of temsirolimus for the treatment of renal cell carcinoma, the frequencies of mucositis, stomatitis, aphthous stomatitis and mouth ulceration were reported as distinct categories, while the differences between these descriptors were not defined.(23) Moreover, mucosal inflammation and tongue ulceration were reported as distinct oral AEs.(24) There is consensus among oral medicine specialists managing patients with oral mucosal lesions associated with mTORIs that the specific term of mTOR inhibitor-associated stomatitis (mIAS) is preferable to the general term oral mucositis which is associated with cytotoxic chemo- and radiotherapy.(22, 25-28)

The newly developed PRO DERETT-P and CRO DERETT-H,(3) wherein common mucocutaneous AEs are listed by subtype, and the modified VHNSS2.0 may be of help in assessing the signs and symptoms of the related AEs in detail.

Generic oral AE scales OMAS and WHO OTS are available, however these are not specific for targeted therapies. No controlled trials have assessed the management of TKI- and mTORI-induced oral AEs as the primary outcome measure. Interventions for persistent TKI- or mTORI-related oral AEs, currently may include corticosteroids and other anti-inflammatory agents as well as supportive treatments such as local anesthetics and antimicrobials.(29)

Chapter 3 addressed the prevention, terming, assessment of AE symptoms and signs, reporting, grading, and treatment of the AE as one entity and by subtype of mTORI-associated mucosal AEs. The objective of this chapter was to provide an up-to-date review of the clinical presentation, terminology, pathogenesis, assessment and management of mIAS and other mTORI-associated oral AEs.

For the prevention of conventional oral mucositis and targeted therapy-associated stomatitis, most recommendations begin with oral care plans coupled with patient education.(15, 30) A range of products are currently in development for the prevention and management of oral AEs that fall into four main categories: cell resistance modifiers, mechanism specific inhibitors, damage control agents, and healing accelerators. However, to date, proven approaches for the prevention and treatment of oral AEs are limited.(30, 31)

Generic and specific CRO instruments are available to assess the incidence of targeted therapy-associated oral AEs. In the majority of the papers the CTCAE grading instrument(12) is used to assess the incidence of AEs, while this instrument is not developed for this purpose. The CTCAE is a blunt instrument, developed to grade the severity of AEs. For assessing the incidence of targeted therapy-associated oral AEs the oral assessment instruments OMAS(14) and WHO OTS(20, 21) are available. Because of the symptoms of targeted agents-associated stomatitis, the modified version of the VHNSS, version 2.0,(3) the mIAS scale(10) and the EA(4) are potentially useful to assess oral AEs. The Bristol Stool Chart can be used to measure the gastrointestinal mucosal injury, namely the consistency of stool to be able to make a distinction between e.g. diarrhea and loose or mushy stool.(2)

We found that a variety of grading scales for staging the severity of targeted therapy-associated mucocutaneous AEs are available, while these scales are rarely used in research and daily practice. There is a gap between the availability and the use of these scales as seen in the literature. Currently, the CTCAE is commonly utilized in oncology clinical trials by clinicians to report overall toxic effects of cancer treatment.(12) Consequently, decisions about dose modifications due to AEs are based on clinician assessment utilizing the CTCAE grading system. It is noted that, despite its widespread use and utility, drawing conclusions out of the CTCAE for the treatment of the AE is sub-optimal, since the CTCAE is not a validated instrument, and has weaknesses in differentiation levels of severity of AE and does not specifically assess the impact on HRQoL.

In **chapter 4** the prevention, terming, assessment of AE symptoms and signs, grading, and treatment of the AEs of chemotherapy, radiation therapy and targeted therapy-associated mucosal injury in the ESMO guidelines was discussed. Accurate assessment of the morbidity of the mucosal AEs will allow for informed decisions on dose modification and interruption, which may have far reaching consequences. The development of specific instruments for targeted therapy-associated mucosal AEs seems justified.

It was found that no controlled trials have assessed the management of targeted therapy-associated mucosal AEs as a primary outcome measure. While there is currently no systemically derived evidence for an approach to management, since targeted therapies are associated with inflammation and localized and systemic infection, mucosal hygiene, anti-inflammatories, and pain management may be considered until a more comprehensive, evidence-based approach has been defined. In the absence of confirmatory data from clinical trials, expert opinion-based recommendations can be considered. These statements reflect the state-of-the-science as it presently exists.(22, 27, 28)

In **chapter 5** we report that xerosis and pruritus have a major negative impact on HRQoL during the first 6 weeks of EGFRI treatment. The objective of this sub-analysis of the BeCet study was to examine HRQoL of patients experiencing skin AEs during the first 6 weeks of EGFRI treatment, using five different questionnaires. AEs were reported in DERETT-P. The impact of EGFRI-associated dermatological AEs on HRQoL was examined using four HRQoL questionnaires; FACT EGFRI-18, FACT-G, SF-36, and the Skindex-16. The findings are congruent with the findings in the STEPP trial.(32, 33) In literature, xerosis and pruritus are less frequently addressed EGFRI-associated skin AEs. As a result, not all patients are counseled about these possible skin AEs before initiating treatment. However, providing patients adequate information about possible AEs and their treatment has shown a positive result on patients' emotional and physical well-being.(34-36) Counseling patients prior to EGFRI treatment about potential xerosis and pruritus is therefore important, as well as taking preventive measures against these AEs.(37-40)

The targeted therapy specific instruments that have been evaluated in these studies, are the DERETT-P,(41, 42) FAST-EGFRI,(7) and FACT-EGFRI-18.(6) The DERETT-P is mainly a symptom and signs scale but includes questions like "which symptoms bothered you most?", "why?", and "How much did the symptoms influence your HRQoL?" The FAST-EGFRI is the preliminary version of the FACT-EGFRI-18 and in this thesis we report the use of an English and Dutch version of the FACT-EGFRI-18. Because measures of HRQL describe the patient's experience as the result of therapeutic care, they are valuable and vital additions to physiological or biological measures of health status.(43) The HRQoL assessment instruments we have used are the SF-36,(36) the FACT-G,(8, 35) and Skindex-16.(17)

There is a discongruity in functional domains in the different scales that were evaluated throughout this thesis. The SF-36 covers eight scales: physical functioning, role limitations due to physical health and due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health.(16) Within the FACT-G the following three HRQoL domains are addressed: physical, emotional, and social well-being /family.(44) Skindex-16 addresses symptoms, emotions, and function,(45) while the FAST-EGFRI and the FACT-EGFRI-18 are constituted by physical, social/emotional, and functional well-being domains.(6, 7) These different

formats complicate the comparison of the outcomes of the different scales and differences between studies.

It was found that there are no reporting instruments available which address solely the AE characteristics. The targeted therapy specific instruments DERETT-P and DERETT-H have items regarding reporting AE characteristics incorporated. The DERETT-P questionnaire also allows report of the severity of the AEs and which AE was most impactful. In the open fields in the diary, patients can elucidate their AEs. In a drawing they can record the site of the AEs; questions about the appearance of the symptoms and signs and the duration of the AEs are incorporated.(3, 41) In addition, the 'objective' reporting of AE characteristics may be supported by photographs, biopsies and swabs.

Evaluation of the outcome of an intervention and education is critical in ongoing care. It was found that no evaluation instruments in the literature exist that specifically address the outcome of the applied measures for targeted therapy-associated AEs. The targeted therapy specific instruments DERETT-P and DERETT-H have evaluation items incorporated, however. Questions about the taken measures and the effect of the taken measures are incorporated in both versions of DERETT.(3, 41)

Chapter 6 addressed the translation and linguistic validation of the FACT-EGFRI-18 instrument from English into Dutch. The translation was accomplished by employing the Functional Assessment of Chronic Illness Therapy (FACIT) multilingual translation methodology. The FACT-EGFRI-18 only evaluates HRQoL and not symptoms, not all skin and mucosal AEs can be assessed, and it is only available for one type of targeted therapy. The above points justify further development of this questionnaire for use in targeted therapy.

Despite the fact that the Dutch version of the FACT-EGFRI-18 seems to be content-wise and linguistically valid (chapter 6), we found in **chapter 7** that from the patients' point of view, the questionnaire can be improved on several points. FACT-EGFRI-18 evaluations show:

1. The FACT-EGFRI-18 provides 17 items addressing the skin and only one item addressing the mucosa.
2. In addition to assessing the impact of the AEs on a patients' HRQoL, patients also felt the need to rate their symptom burden. The patients' natural inclination was to rate the prevalence, intensity, and duration of the symptoms rather than the extent to which it interfered with HRQoL, based on the interpretation of the questions.
3. Some inconsistencies between numerical rating and the associated comments suggest that clear instructions regarding completion of the instrument needs to be provided.
4. Six out of the ten patients gave feedback that not all the skin and mucosal AEs were included in the questionnaire. Questions regarding sensitive eyes, a runny nose, bloody or crusty nasal cavity due to pimples, dry mouth, tickling and

tingling sensations, pain touching the hair, and some space for additional comment were mentioned by the participants as items that should be incorporated into the questionnaire.

5. Patients reported difficulties in 5 of the 18 items pertaining to the location and the relationship of the skin and mucosal AEs with EGFRI treatment; e.g. how a flaky scalp should be scored if a patient already experienced dandruff, and how to respond on the question about the interference with household tasks when the patient does not do any, but is bothered by sensitivity around the fingernails.
6. The partner/child of a patient noticed that there was a greater impact of the symptom burden on the HRQoL than the patient rated. While patients stressed being grateful for receiving anticancer treatment, their families appeared to be more focused on the HRQoL of the patient including skin and mucosal AEs.
7. Patients expressed an appreciation for the opportunity to discuss their difficulties coping with their skin and mucosal AEs.

The above points justify further development of this questionnaire for use in targeted therapy. Additional mucocutaneous AE items in combination with symptom assessment will provide more complete information. Since skin and mucosal AEs are also elicited by other targeted anticancer therapies such as non-EGFRI tyrosine kinase inhibitors, mTORI, immuno-oncology and BRAF inhibitors, it would be worthwhile to develop a questionnaire suitable for all these targeted agents instead of only for EGFRIs.

In the various articles for this thesis, one or more of the six components of a systematic AE approach are addressed. In addition, the preventive measures including education, AE terminology, assessment of the AE symptoms and signs, reporting the AE characteristics, grading the severity of the AEs, evaluating and (re-) education about the taken AE measures, and AE treatment are discussed. **Table 1** provides an overview of AE steps referred and studied in each manuscript. As outlined in **Table 2**, there are instruments developed to assess targeted therapy-associated AEs by PRO and CRO. In addition, instruments not specific developed for these agents can be considered for use as well.

Future perspectives

The approach to AEs and effective prevention and treatment of AEs are an important part of the optimal treatment for patients receiving targeted therapies. Figure 1 uses this base and illustrates a new model of a patient-driven AE co-care approach.

Patients and HCPs start and end the AE approach together, while the assessments before and during therapy can be performed separately but in close collaboration with each other, yielding more comprehensive evaluation and leading to improved

TABLE 1. Overview of the adverse event steps referred and studied in each manuscript

Chapter	**Adverse Events**		**Education**	**Terming**	**Assessment** Symptoms & Signs of AEs			**Reporting**	**Grading** AE Severity		**Evaluation**	**Treatment**
	skin	mucosal	preventive measures	AEs	by CRO	by PRO	impact on HRQoL	AE characteristics	by CRO	by PRO	taken measures	AEs
2. Oral AE's associated with TKI & mTORI in RCC	referred (2)*	studied (11)*	no	studied	studied	studied	no	no	studied	referred	no	referred
3. mTORI-associated stomatitis	no	studied (7)*	studied	studied	studied	studied	no	referred	referred	referred	no	referred
4. Management of oral & gastrointestinal mucosal injury: ESMO Guideline	referred (1)*	studied (3)*	studied	studied	studied	studied	no	no	studied	studied	no	studied
5. Xerosis & pruritus as major EGFRI-associated AE's	studied (29)*	studied (10)*	referred	studied	referred	studied	studied	studied	referred	studied	referred	referred
6. Translation & linguistic validation FACT-EGFRI-18	studied (17)*	referred (1)*	no	studied	no	studied	studied	no	no	no	no	no
7. Experiences with the FACT-EGFRI-18	studied (17)*	referred (1)*	no	studied	no	studied	studied	no	no	studied	no	no

AE = adverse event, HRQoL = Health Related Quality of Life, CTCAE = Common Terminology Criteria for Adverse Events; CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; TKI = tyrosine kinase inhibitor; RCC = renal cell carcinoma; mTORI = Mammalian Target of Rapamycin Inhibitor; EGFRI = Epidermal Growth Factor Receptor Inhibitor; *= number of AEs addressed; AEs = adverse events; CRO = clinician rated outcome; PRO = patient reported outcome; HRQoL = Health Related Quality of Life; light grey = referred; dark grey = studied

TABLE 2. Instruments that may be used to chart targeted therapy-associated adverse events

Instruments	**Adverse Events**	**Education**	**Terming**	**Assessment AE Symptoms & Signs**			**Reporting**	**Grading AEs**		**Evaluation**	**Treatment**
	addressed	preventive measures	AEs	by CRO	by PRO	impact on HRQoL	AE characteristics	severity by CRO	severity by PRO	taken measures	AEs
Specific developed for targeted therapies	Generic										
	Skin										
	Mucosa			mIAS scale	modified VHNSS2.0 mIAS scale EA			mIAS scale	modified VHNSS2.0 mIAS scale		
	Muco-cutaneous			Derett-H	Derett-P FACT-Egfri18 FAST-Egfri	Derett-P FACT-Egfri18 FAST-Egfri	Derett-P Derett-H	Derett-H MESTT	Derett-P	Derett-P Derett-H	
General or developed for other treatments	Generic	MOATT				SF-36 FACT-G		CTCAE	PRO-CTCAE		
	Skin					Skindex-16					
	Mucosa	Oral Care protocol		OMAS WHO OTS	VHNSS2.0 Bristol Stool chart			OMAS WHO OTS			
	Muco-cutaneous										

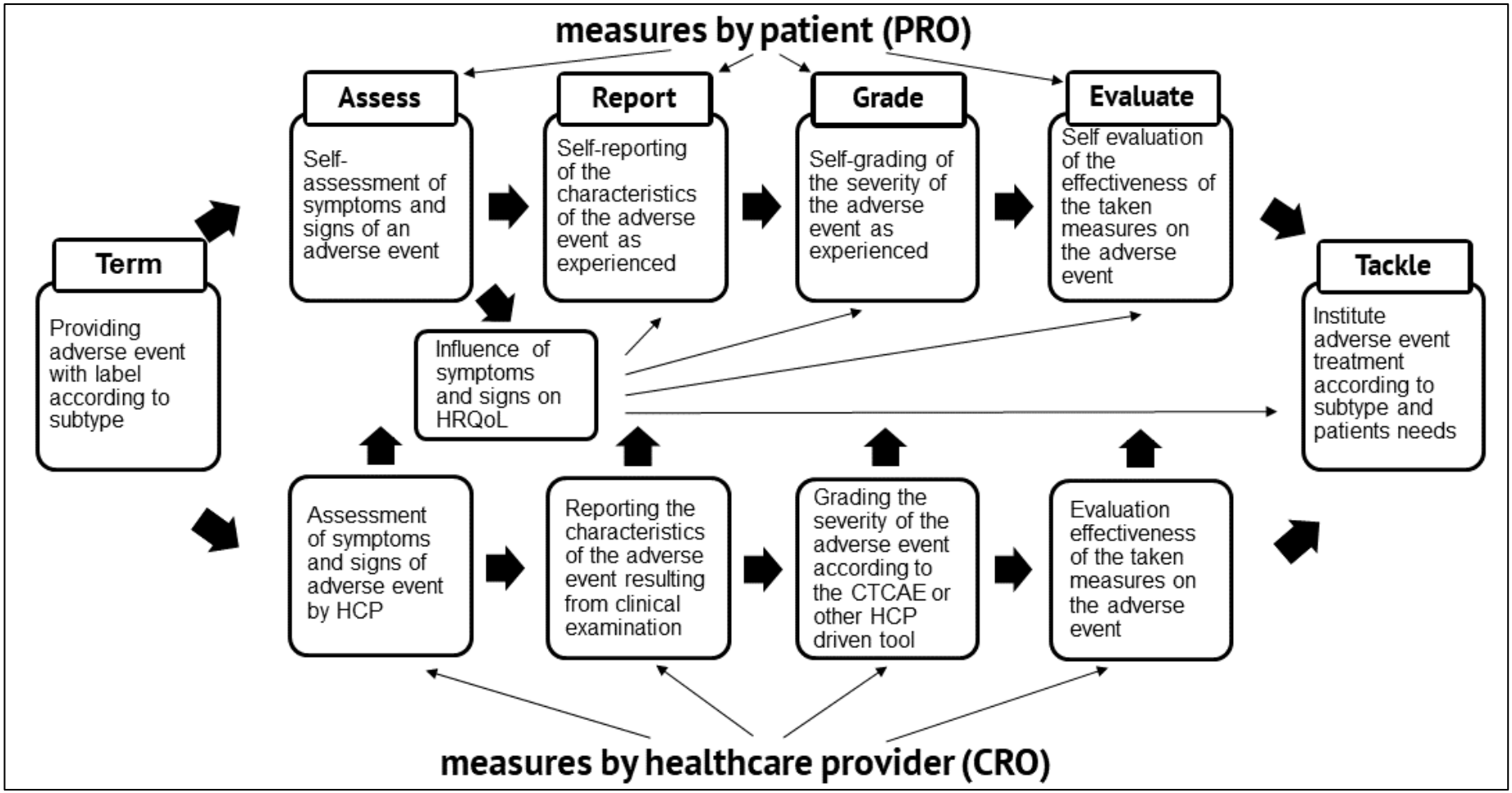
AEs = Adverse Events; CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; HRQoL = Health Related Quality of Life; MOATT = MASCC Oral Agent Teaching Tool(11); Oral Care Protocol(15); mIAS scale = mTOR Inhibitor Associates Stomatitis(10); Derett-H = Dermatological Reactions Targeted Therapy-Healthcare Professionals(42); OMAS = Oral Mucositis Assessment Scale(14); WHO OTS = World Health Organization (WHO) Oral Toxicity Scale (OTS)(20, 21); Modified VHNSS2.0 = modified Vanderbilt Head and Neck Symptom Survey version 2.0(3); EA = Experimental Assessment(4); Derett-P = Dermatological Reactions Targeted Therapy-Patients(41); FACT-Egfri-18 = Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18(5); FAST-Egfri = Functional Assessment of Side Effects to Therapy-Epidermal Growth Factor Receptor Inhibitor(7); VHNSS2.0 = Vanderbilt Head and Neck Symptom Survey version 2.0(18); Bristol Stool Chart(2); SF-36 = Short Form Questionnaire(36); FACT-G = Functional Assessment of Cancer Therapy - General(8); Skindex-16 = Skin Index(17); MESTT = MASCC EGFRI Skin Toxicity Tool(46); CTCAE = Common Terminology Criteria for Adverse Events.(12); PRO-CTCAE = Patient-Reported Outcomes version of the CTCAE(13, 47)

outcomes. Patients report AE characteristics and severity, the effect of AE measures and the AE treatment they desire. Patients also report the impact of the AEs on their HRQoL. The HCP is supportive to the patient. At initiation of a new treatment, the patient may need guidance from the HCP in approaching AEs, since the HCP may be expected to be experienced and provide guidance & support where necessary. When a treatment becomes more chronic, a patient will may become more experienced and therefore less dependent on the HCP's support in measuring AEs. For obtaining some AE treatments, patients may be independent of the HCP, e.g.: obtaining hemorrhoid cream, foot salt, vinegar, insoles, and mouth rinses. Other treatments may require the HCP such as for receiving prescription when needed e.g.: antibiotics and corticosteroids. The concept is a co-care model while on chronic targeted therapy treatment, wherein the patient is leading the process and the HCP supports where appropriate.

By following the six steps described, terming, assessing, reporting, grading, evaluating, and treating AEs by their subtype, the scope of the AEs may become more apparent. For both the patient and the HCP, choosing the most appropriate treatment is facilitated by taking these six steps which provides a roadmap that supports the implementation of appropriate treatment options for AEs associated with targeted anticancer therapies.(3) The instruments that may be used to chart targeted therapy-associated AEs are shown in Figure 2. The top of the figure shows the instruments that may be used by the patient while the body of this figure shows the instruments that may be used by the HCP.

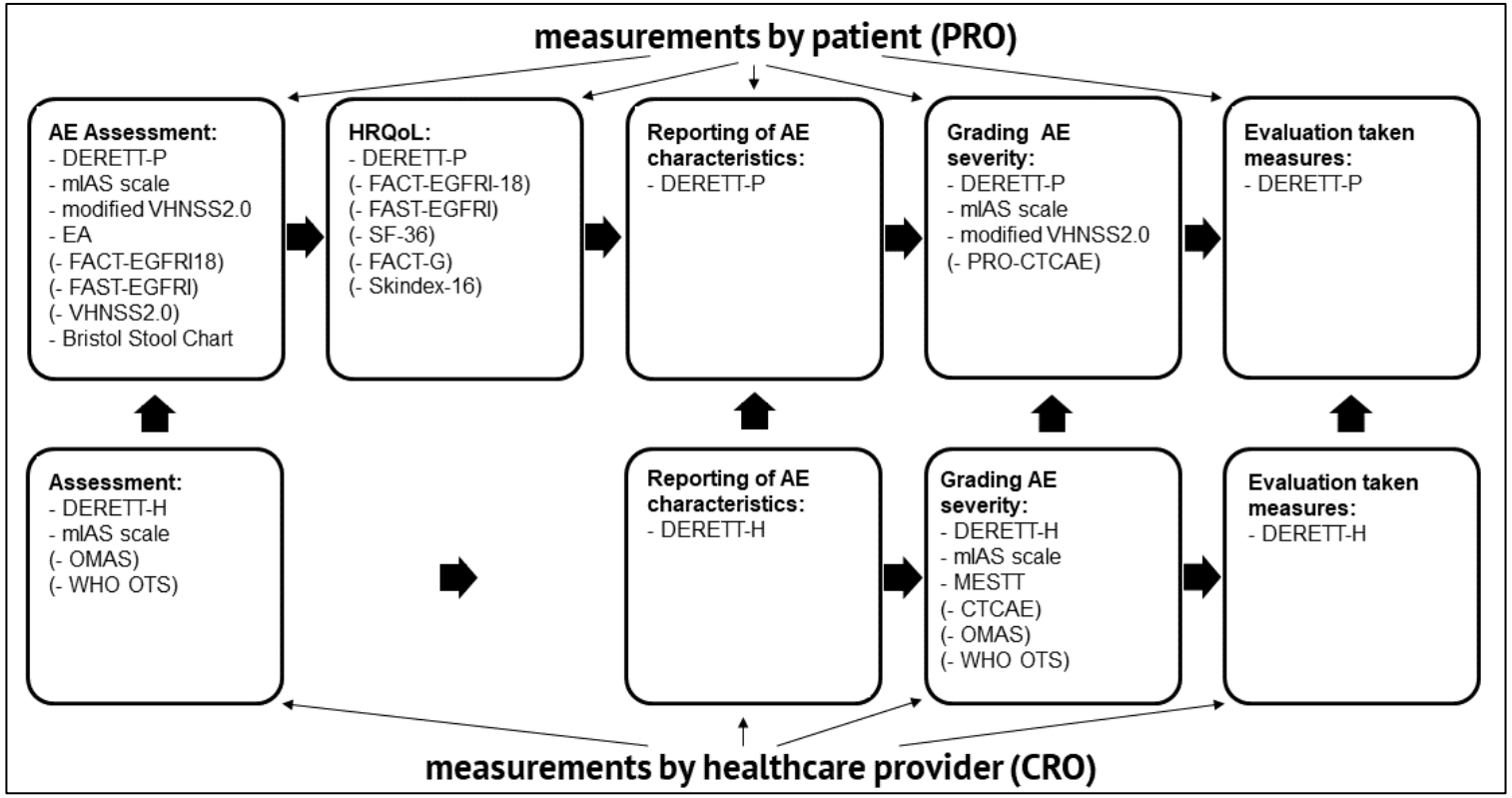
A growing number of patients with cancer will be treated with targeted agents, most frequently as outpatients and over a long time span. Targeted therapies are high cost medications.(48) The cost of targeted therapies is an important consideration, particularly when compared to some traditional chemotherapies. Additional treatment costs include the costs to get all stakeholders trained about effective AE management. Further costs are costs to treat AEs and costs for treatment modifications. This indicates a need for awareness and early recognition of AEs among the patients, oncologists, oncology nurses, dental professionals, dermatologists, pharmacologists, pharma representatives, and basic scientists but also among community HCPs, such as primary care doctors, primary care nurses, dental professionals, and allied health professionals. Scientific knowledge does not, by itself, result in widespread implementation and social impact. The research from the clinic must be translated into practical use. Valorisation is the impact that can be created through the transfer of scientific knowledge.(49) Examples include developing an assessment instrument or applying scientific knowledge to a system or process which can be disseminated through a training program. Some of our findings show high potential for valorisation.

FIGURE 1. Proposed new patient-driven co-care model of approaching adverse events



CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; CTCAE = Common Terminology Criteria for Adverse Events; HCP = healthcare provider

FIGURE 2. Instruments that may be used to chart targeted therapy-associated adverse events



AEs = Adverse Events; CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; HRQoL = Health Related Quality of Life; mIAS scale = mTOR Inhibitor Associates Stomatitis(10); Derett-H = Dermatological Reactions Targeted Therapy-Healthcare Professionals(42); OMAS = Oral Mucositis Assessment Scale(14); WHO OTS = World Health Organization (WHO) Oral Toxicity Scale (OTS)(20, 21); Modified VHNSS2.0 = modified Vanderbilt Head and Neck Symptom Survey version 2.0(3); EA = Experimental Assessment(4); Derett-P = Dermatological Reactions Targeted Therapy-Patients(41); FACT-Egfri-18 = Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18(5); FAST-EGFRI = Functional Assessment of Side Effects to Therapy-Epidermal Growth Factor Receptor Inhibitor(7); VHNSS2.0 = Vanderbilt Head and Neck Symptom Survey version 2.0(18); Bristol Stool Chart(2); SF-36 = Short Form Questionnaire(36); FACT-G = Functional Assessment of Cancer Therapy - General(8); Skindex-16 = Skin Index(17); MESTT = MASCC EGFRI Skin Toxicity Tool(46); CTCAE = Common Terminology Criteria for Adverse Events(12); PRO-CTCAE = Patient-Reported Outcomes version of the CTCAE(13, 47).

An assessment and grading instrument wherein the presence of AEs and their impact upon HRQoL are incorporated should be developed. As more and more patients will be treated with targeted therapies, alone or in combination with cytotoxic and immunomodulatory medications, it will become increasingly important to understand the multidimensional experiences of AEs. This is an important challenge for patients and HCPs in their effort to assess AEs. Therefore, in this thesis, in addition to assessing the symptoms and signs of the AEs, the influence of the AEs on the HRQoL are addressed and a conceptual co-care model of a patient-driven approach to AEs of targeted therapies is presented.

A continuing concern is the use of the CTCAE instrument since it is still commonly utilized in oncological clinical trials to assess adverse events of cancer treatment.(12) However, most CTCAE items are not specifically developed to grade the severity of targeted therapy-associated AEs and therefore the CTCAE is not recommended for direct application for assessment of targeted therapy-associated AEs. Development of a comprehensive grading system similar to the MESTT(9, 46) seems appropriate for staging the severity of targeted therapy-associated AEs by CRO. DERETT-H has mucocutaneous AE grading items incorporated as well.(42) Grading of the severity and impact of the AEs by the patients themselves as outlined in the AE co-care model may improve diagnosis and management of these specific reactions. For the mucocutaneous AEs DERETT-P seems suitable. For other AEs, a grading tool needs to be developed.

As outlined in chapter 7, the study participants felt the need to rate the experienced mucocutaneous AEs instead of the influence of the mucocutaneous AEs on their HRQoL. Therefore a combined assessment and grading instrument should be developed. When patients can separately rate the mucocutaneous AEs and their influence on their HRQoL, they may be able to better capture the effects upon HRQoL. AEs may be assessed in a three-part scale that may measure:

1. if an AE developed (appearance symptoms & signs)
2. the intensity/severity of the AE (grading)
3. if the patient is distressed/suffers from it (impact AE on HRQoL)

The proposed questionnaire is modeled in Table 3.

To be able to develop evidence based guidelines for the prevention and treatment of targeted therapy-associated AEs, more research in this area is needed. As outlined in chapters 2, 3 and 4 there is currently scant AE evidence upon which to build evidence-based guidelines. More evidence is needed since guidelines based on expert opinion are scientifically not ideal. However, until clinical trials establish evidence base clinical experience, expert opinion is the best available guidance.

By empowering patients to be more involved in their treatment and in the approach of targeted therapy-associated AEs, the entire interdisciplinary team may help patients maintain their HRQoL, promote treatment adherence, and support completion of

TABLE 3. 3-part adverse event assessment and grading instrument

	Was, or is, this symptom or sign present?	Complete only when marked 'yes', so when you **EXPERIENCED** the mentioned symptoms or signs	
		On a scale from 0 – 10, what was the **SEVERITY** of these symptoms or signs at their worst, according to you?	On a scale from 0 – 10, how much did these symptoms or signs **INTERFERE** with your usual activities?
symptoms & signs	Yes/No	0 = not at all; 10 = very severe	0 = not at all; 10 = very much
symptom 1	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
symptom 2	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
symptom 3	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
sign 1	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
sign 2	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
sign 3 etc.	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Y = yes; N = no

cancer treatment as planned. Well-designed trials with appropriate terminology, assessment and grading instruments wherein the AE treatment response is the primary outcome measure can bring the evidence desired by patients, HCPs, pharmaceutical companies and the society at large, to bring more HRQoL, enhanced treatment outcome and to conserve resources.

For the generation of a patient-driven AE conceptual co-care model, the critical items are derived from questionnaires and case report forms used in clinical targeted therapy trials.(6, 32, 33, 50-55) For the identification of terms used in patient files the medical records of oncology patients on targeted agents in the Waterland Hospital in Purmerend, The Netherlands were searched systematically from March 2009 until March 2014. Terminology used to describe AEs and recorded missing information has been evaluated in detailed AE diagnoses. Terms were identified in prior grading instruments.(9, 12, 46) The identified components for a systematic, patient-driven targeted therapy-associated AE approach can be summarized in 6 steps:(1, 3)

1. Terming – the establishment of the diagnosis of the AE by subtype
2. Assessing – the identification of symptoms and signs of the AEs and the impact of such an event on a patients' HRQoL
3. Reporting – the collection and reporting of in-depth characteristics of the AEs
4. Grading – the classification of the severity of the AEs
5. Evaluating – the exploration of the taken measures and discussion about the treatments to be initiated
6. Treating – the institution of the most appropriate and effective AE treatment.

The AE management skill is an important competency since there can much be achieved by individuals. However, competencies in AE management alone will not make a sustainable difference for society at large. Competencies in several distinct core areas may improve cancer treatment outcomes. Recommendations include developing:

1. explorative AE trials in a structured way in early phase drug development (phase I and II),
2. long-term advisory boards, steering committees, summits, and roundtables,
3. interdisciplinary teams with key disciplines involved,
4. thorough training of pharma, pharmacists, HCPs and patients,
5. patient centered drug launches, and
6. easy, understandable patient information written in the same format as the HCP information.

These seven measures may promote adherence to the cancer medication, resulting in improved patient outcome.

The work in this thesis lead to recommendations to develop collaboration with patients. The conceptual co-care model of a patient-driven approach to AEs of targeted agents in oncology may be complemented with a 3-part adverse event assessment and grading instrument, evidence based AE treatment guidelines, and obligated educational programs on the AE core competencies, and applied.

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