Financial effects of a tumor disease – Development and validation of a patient reported outcome measure in Germany: Study Protocol

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Abstract

Introduction

Financial toxicity as an individual consequence of a cancer diagnosis currently evolves to a clinically relevant patient-reported outcome, as several US studies showed that financial burden from cancer patients could impact the quality of life and mortality significantly. However, there is only limited data about financial burden on patients from universal healthcare countries and, in particular, Germany. One reason for this is the lack of a standardised and validated German-language survey instrument to measure financial toxicity precisely. This study aims to develop such an appropriate instrument.

Methods and analysis

The project is structured into three phases. The first phase aims to determine the construct definition of financial toxicity and to further evolve the existing framework. Semi-structured interviews with patients and focus groups with representatives from social services and HTA-institutions/payers are conducted to determine domains of financial toxicity in Germany and methodological requirements of a new instrument. Additionally, a systematic literature review is performed to identify risk factors associated with financial toxicity in third party payer systems. Based on the results, the second phase focusses on the development and validation of the intended instrument measuring financial toxicity. The finalised draft of the instrument is tested regarding its reliability, validity and test fairness by surveying it in at least n=400 cancer patients in Germany. The third phase addresses the application of financial toxicity as a clinically relevant patient-reported outcome in practice. It refers to the clinical (screening tool for social services) and regulatory context (payers/HTA-institutions).

Ethics and dissemination

This research as part of the project “Financial effects of a tumor disease“ is funded by the German Cancer Aid (Deutsche Krebshilfe), grant number: 701134038. Ethical approval is confirmed by the local Ethics Committee of the Medical Faculty of the University of Heidelberg and acknowledged by the Ethics Committee of the University Hospital Jena. Obtained data could contribute to better understand, communicate and address financial impact in the future, e.g. by offering targeted support or considering financial effects in health technology assessment.

Trial registration number

NCT05319925

Introduction

The financial impact of cancer on the individual patient is only slowly moving into the public focus, although social services have been recognising an increasing need for guidance in this area for years. Cancer diagnosis and therapy can be linked to physical, emotional and even financial burdens in patients [1]. Financial burdens not only include direct medical and non-medical costs of treatments, but also indirect costs such as loss of income [2]. Financial burden and its consequences were first discussed in the US healthcare setting, where the phenomenon was described as 'financial toxicity'. Until today, most studies on financial toxicity were conducted in the US, demonstrating a prevalence of financial toxicity among cancer patients ranging from 39% to 64% as a recent systematic review highlighted [3]. Available US studies showed that cancer patients experience financial difficulties from their co-payments during treatment, which may result in delay of their treatment [4], lower quality of life, greater incidence of depression and anxiety [1,3,5,6] and even an increased mortality [7].

However, the transferability of these data to other jurisdictions is limited due to different designs of healthcare systems. First studies from third party payer healthcare systems confirmed the prevalence and outcomes from the US to some extent. A recent review by Longo et al [8] in publicly funded healthcare systems discovered a prevalence of 7% in Australia to 39% in Ireland. In Germany, a qualitative study showed that one third of the patients questioned, reported a deterioration in their financial situation after the cancer diagnosis [9]. A recently published study has shown that many German cancer patients are confronted with relatively high additional expenses due to their illness [10].

In more detail, explicit data from Germany confirmed financial burdens of oncological patients due to rising costs: In a pilot study at the National Center for Tumor Diseases (NCT) Heidelberg, 156 patients were asked about changes in their income since they were diagnosed with cancer, with 75% reporting a deterioration in their financial situation and 60% reaching a total loss of 500€ per month [11]. In a further prospective cohort study [12], 247 cancer patients were asked about changes in their financial situation after the diagnosis and the start of therapy. It was found that 81% of the patients have additional expenses as a result of the cancer disease, which for most of those affected (76%) is less than 200€ per month. 37% of respondents suffered a loss of income, which amounts to 501-1,200€ per month for a third (36%) and more than 1,200€ per month for a quarter (24%). As a consequence, 40% state that they put money aside in everyday life. Multivariate analyses significantly determined that high income losses and/or additional expenditure are associated with poorer quality of life and higher distress. However, evidence from Germany about the financial situation of patients with and after cancer and its associated socio-economic effects remains limited. One reason for this is, that there is no standardised and validated German-language survey instrument.

Systematic reviews pointed out the heterogeneity of the constructs and methods applied to measure financial toxicity [13,14], as most of the currently available studies used non-validated questionnaires in small populations. In 2014, Souza et al [15] introduced the first cancer-specific survey instrument "COST" and in 2017, the questionnaire was validated in the US [16]. However, the suitability of the instrument in other jurisdictions reminds also unknown as the transferability of a US-specific instrument to third party payer systems might be limited due to country-specific factors influencing financial burdens. In most studies (incl. Germany), financial distress is thus still assessed by a subscale of a patient-reported outcome measure, mostly the EORTC-QLQ30 questionnaire, with a different focus (often HRQoL), which do not exhaustively capture the construct of financial toxicity.

This study aims to develop and validate a standardised German-language instrument for measuring self-reported financial effects of a tumor diagnosis and therapy ("FIAT") in a cross-sectional bi-center study. The project is an interdisciplinary approach incorporating expertise of representatives of the

fields of oncology/medical ethics, health economics and methods in empirical social research as well as experts of social services and payers/HTA-institutions. The new instrument is tested in practice by additionally piloting a screening program in everyday counselling to identify patients with a particularly high risk of financial burden. Obtained data will make the patient-related description of financial difficulties more comprehensible, communicable and addressable in the future, e.g. by offering targeted advisory aids or considering financial effects in health technology assessments. A systematic recording and open discussion of the financial effects of illness and the associated burdens within the German care system can also help to moderate a policy discussion on the payers´ side.

Methods

The development of the planned instrument follows the recommendations of the German Data Forum [17] and is guided through an interdisciplinary research team from the fields of oncology/medical ethics, health economics and methods in empirical social research. The project encompasses three project phases with an overall of six work packages (WP). Each WP is led by one or two network partners. The duration of the project is 36 months. A short overview of all study phases is provided in Graph 1. In the following, tasks and expected results for each WP are explained.

Phase	Task	WP	Aim	Method
1	Needs Assessment Patients	1	To understand dimensions of financial impact of cancer for the affected patients in Germany	Semi-structured interviews with cancer patients
	Needs Assessment social services, third-party payers and HTA institutions	2	To determine requirements and applicability of a patient-reported instrument from the perspective of potential user groups	Focus group with representatives of: a) Social service b) Third-party payers and HTA institutions
	Systematic literature review	3	To analyse risk factors of experiencing subjective financial effects	Systematic literature review
2	Questionnaire Piloting and Validation	4	To test the comprehension of developed questions and to validate the finalised instrument	Cognitive pre-test and validation study
3	Piloting of a screening program for social services	5	To implement the instrument in the routine counselling of a social service	Pilot study evaluated through semi-structured interviews with patients and social service representatives
	Recommendations for the use of the measuring instrument	6	To develop recommendations for further applications of the questionnaire	Evaluation of previous WP's

Phase 1: Construct definition and item generation

In the first study phase, preliminary studies are performed throughout three WPs to identify dimensions, topics and risk factors that are relevant for the assessment of financial effects in cancer patients. Results are used to define the construct of financial effects and to generate a list of appropriate indicators for measuring financial effects in order to derive a pre-final questionnaire.

Needs Assessment patients (WP 1)

The needs assessment of WP 1 aims to understand the dimensions of financial effects of cancer for the affected patients in Germany. 15-20 semi-structured interviews with patients are conducted in two local clinical centers in Germany. The following eligibility criteria for study inclusion are applied: patients at least 18 years old with any type of historically or cytological confirmed solid cancer or haematological malignancy with an ECOG-Status <2, who have undergone at least two months of cancer related therapy. Eligible patients sign an informed consent form for participation. Each interview lasts approximately 30-60 minutes and is audio-recorded. A guideline for the semi-structured interviews is developed based on results of previous studies. Interviews are conducted until informational saturation is reached. The sample is based on a theoretical sampling-strategy

considering the following personal characteristics: Employment (self-employed/not self-employed) and type of insurance (statutory/private). Audio records are transcribed and a qualitative content analysis of the interviews is performed to systematically identify relevant dimensions and topics for patients regarding their tumor disease-specific financial effects.

Needs Assessment social services, third-party payers and HTA institutions (WP 2)

The needs assessment of WP 2 aims to determine requirements and applicability of a patient-reported instrument for financial effects of cancer from the perspective of potential user groups of that instrument, namely social services, third-party payers and HTA institutions. Two qualitative focus groups of 1) social services and 2) third-party payers and HTA institutions are conducted whereby each focus group persists of four to six experts. Participants sign a written consent in advance. Focus group sessions in form of a guided group discussion with a duration of two hours are performed and audio-recorded. Beforehand, guidelines for each focus group are developed by considering previous studies and the individual study aim of each focus group due to the stakeholders involved. Social service employees are considered eligible for participating in the first focus group, if they work with cancer patients in everyday counselling. The second focus group persists of relevant representatives of third-party payers and HTA institutions in Germany, namely representatives of the Federal Joint Committee (G-BA), the Institute for Quality and Efficiency in Health Care (IQWiG), and the National Association of Statutory Health Insurance Funds (GKV-SV). Eligible participants work in one of the relevant institutions and are familiar with the German HTA processes for new pharmaceutical products and/or patient-reported outcomes. Audio-records are transcribed and a qualitative content analysis is performed in regards to the individual study aim of both focus groups from a regulatory perspective.

Systematic literature review (WP 3)

A systematic literature review (SLR) following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18] is conducted to identify underlying risk factors of patient reported financial distress due to a cancer diagnosis and therapy in high-income countries with universal healthcare coverage. Search is performed in PubMed, Psycinfo and CINAHL considering publications until December 2020. Due to expected heterogeneity of the studies, a qualitative synthesis is undertaken in terms of the underlying aims of the SLR. Results of the SLR are used to a) inform a definition of individual financial effects to derive the underlying construct, b) examine the degree of potential factors influencing subjective financial effects that need to be considered in further analysis and c) identify possible items for a measurement of subjective financial effects.

Construct of financial effects

In order to address all relevant dimensions and topics and to measure financial effects of cancer patients precisely, the construct of financial effects is defined at the end of phase 1. Hereby, results from study phase 1 are linked to the previous overview work on methods for measuring financial toxicity [13]. The definition of financial effects is derived and the conceptual framework including all relevant subdomains is defined. The construct is discussed within the interdisciplinary research team and any dissent is solved by consensus.

Item generation

The item generation is performed though a qualitative analysis of the presented results from the needs assessment of patients (see WP 1), social services, payers and HTA-institutions (see WP 2), systematic literature review (WP 3) and recently developed framework of financial toxicity by Witte et al [13] to identify relevant dimensions and topics of financial effects for cancer patients. A list of appropriate items is generated, questions are clustered and a suitable pre-final questionnaire is structured. Afterwards, the pre-final questionnaire is peer-reviewed by the interdisciplinary project team to ensure a) that the questions formulated sufficiently cover the dimensions of the construct, b)

consistency within the construct definition and c) practical applicability for targeted patients; Any dissent is solved by consensus.

Phase 2: Questionnaire Piloting and Validation

Cognitive pre-test

A cognitive pre-test of the draft questionnaire is conducted to examine comprehensibility of questions as well as response options and to identify any potential problems that respondents would have answering the questionnaire. The conduction and analysis of the cognitive interviews is commissioned to an institute with expertise in this field. Cognitive interviews with a duration of approximately 60 minutes are conducted. Eligible patients are at least 18 years old, have any type of historically or cytological confirmed solid cancer or haematological malignancy with an ECOG-Status <2 and have undergone at at least two months of cancer related therapy. The sample is based on a quota-sampling strategy considering the following personal characteristics: Sex (women/men), age (<63 years/>63 years) and education (A-levels or higher/lower than A-levels). Two local clinical centers recruit patients from the day care unit, ambulances or the oncological ward for the cognitive interviews. Participating patients, who have given their written consent, first complete the questionnaire themselves and answer questions of the interviewer about the questionnaire later. A guideline for the cognitive interviews is developed in cooperation between the project team and the conducting institute in advance. This guideline contains questions of the questionnaire for which the research team anticipates possible comprehension problems as well as different probing questions. Probing techniques, like “comprehension” or “category selection probing” [19] are used. A qualitative content analysis is conducted including a systematic recording of the respondents' problems related to comprehension and response. The questions undergo a revision based on the results of the analysis and the results are used for further optimising the first draft of the questionnaire. The optimised pre-final questionnaire is discussed within the interdisciplinary research team regarding suitability of adjustments made in line with the developed construct of financial effects; Any dissent is solved by consensus.

Quantitative evaluation and validation

The newly developed questionnaire is tested in a validation study regarding the distribution parameters of the indicators and their measurement characteristics, the reliability and validity as well as test fairness of the instrument. All steps of development and validation of the instruments are conducted according to the standards of German Data Forum [17]. The validation study is conducted in two steps using two self-administered quantitative paper-pencil surveys with a duration of approximately 30 minutes. In the first step, the pre-final questionnaire is tested to identify problematic questions and to further optimise the instrument by reformulating or excluding certain questions based on preliminary quantitative analyses. After adjustment, the revised version is applied and validated in a second study. Participants of the first study (n=100) are surveyed again within the second study while data of the additional participants in study two are measured at a single time point. A total of n=400 patients in both study phases are recruited from two local clinical centers from the day care units, ambulances or the oncological wards. Additionally, to increase the number of participants for the validation in study two, a web survey is used to supplement the paper-pencil surveys. Patients are considered eligible if they meet the following criteria: at least 18 years old, any type of historically or cytological confirmed solid cancer or haematological malignancy with an ECOG-Status <2 who have undergone at least two months of cancer related therapy.

Distribution and item analyses

To evaluate measurement properties of each single item, distribution and item analyses are applied. The analyses provide information on the distribution parameters of the indicators (correspondence to the normal distribution; skew and excess with evidence for possible ceiling and floor effects) and

measurement characteristics of the individual items (item variance, difficulties, item-total correlations, homogeneity).

Construct and criterion validity

The validity evaluation includes an assessment of convergent and divergent (construct) as well as criterion validity. To investigate construct validity, instruments measuring similar as well as unrelated concepts (nomological network) are defined, based on results available in the literature. Furthermore based on the results in the literature and the results of the systematic literature review [20] criteria (external concepts and variables that are affected by the financial burden) are selected for investigating criterion validity. For example, recent studies found that high financial burden is associated with worse quality of life (measured by the EORTC-QLQ-C30) [21] as well as anxiety and depression (measured by HADS) [22,23]. Construct and criterion validity is assessed by examining bivariate correlations between the subscales of the newly developed instrument and the predefined instruments. Instruments used to determine convergent and criterion validity are expected to have high correlations with subscales of the newly developed instrument. In contrast, instruments used to determine divergent validity should have low correlations with the newly developed questionnaire. In the second step validity is further evaluated by means of a Structural Equation Modelling (SEM) based on the congeneric measurement model within the frame of latent variable modelling (LMV) [24].

Factorial validity

Exploratory Factor Analysis and, additionally for the second study, Confirmatory Factor Analysis are used to analyse the factorial structure of the instrument in order to investigate which theoretically defined properties of the construct can be adequately covered and differentiated with help of single indicators.

Reliability

Data from the first 100 respondents are used for an initial examination of the reliability with Guttmans-Lambda [25]. In the second step reliability is further evaluated by means of a Structural Equation Modelling (SEM) [24].

To evaluate test-retest reliability, the patients of the first survey are re-interviewed in the second survey. Bivariate correlations between the measurements between the first and second survey are obtained.

Test-fairness

Another aim is that the group membership of the target persons (e.g. gender, education, duration or type of disease) does not distort the measurement. To evaluate this property, measurement invariance between these groups [26] is evaluated by means of Multi-Group Confirmatory Factor Analysis (MG-CFA) [27,28], which meets the requirement of test fairness.

Phase 3: Further applicability of the questionnaire

After validation of a new standardised instrument, further application in practice needs to be evaluated. In order to derive profound recommendations for reasonable use of the instrument in different settings, mainly in clinical and regulatory contexts, a pilot study of a screening program for social services is performed and results of all previous WP are further evaluated.

Piloting of a screening program for social services (WP 5)

WP 5 aims to pilot a screening program for social services to identify patients with a particularly high risk of financial burdens. The new developed and validated measure is implemented in the context of routine initial counselling of cancer patients at a participating social service located at a large university hospital in Germany. The instrument is used by the social service as a screening tool over a duration of four month. Afterwards, the screening program will be evaluated through semi-structured interviews

with two to three representatives from social services and eight to ten semi-structured interviews with patients. Developed guidelines for semi-structured interviews are informed by findings of the previous study phases and the study aim of applicability in routine care. Participants sign a written consent form beforehand and the interviews are audio-recorded. The records are transcribed and the data is analysed based on a qualitative content analysis regarding the instrument's comprehensibility, acceptance and effectivity as an early detection instrument for patients at high risk of financial effects.

Recommendations for the use of the measuring instrument (WP 6)

Based on the previous results of the needs assessment with different stakeholders (patients, social service, third-party payers and HTA-institutions) in Phase 1 and quantitative data collection with the introduced instrument of Phase 2 and first insights of a screening program in routine initial counselling from a social service in Phase 3, recommendations with respect to the possible applicability of the instrument in clinical settings (e.g. as an early screening tool for social services) as well as in the regulatory context (e.g. HTA and reimbursement process) are provided. Suitable recommendations are determined through socio-empirical and normative analyses of previously generated results in terms of practical considerations in clinical settings and possible reference points from a regulatory perspective. Recommendations are discussed collaboratively within the interdisciplinary research team and final recommendations will be recorded.

Ethics and dissemination

The study is conducted in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice and all legal and regulatory obligations of the participating country.

Ethical considerations

Ethical approval is confirmed by the local Ethics Committee of the Medical Faculty of the University of Heidelberg and acknowledged by the Ethics Committee of the University Hospital Jena. The study protocol is registered under S-177/2021. Any changes of the study protocol require approval of the involved ethics committees and submission to the funder of the study. The qualitative interviews and focus groups, cognitive pretest and quantitative surveys only take place if the participants have given their informed consent. Participants are informed about the nature and scope of the planned study in advance.

Data protection

Personal data is collected under the recognition of medical confidentiality and the provisions of the General Data Protection Regulation (DSGVO) and the state or Federal Data Protection Act (LDSG or BDSG). Collected data is stored on data mediums of the data centers of University of Heidelberg and Bielefeld that are secured against external access. The personal data is stored only as long as it is required by the purpose of the study or the data is anonymised, but latest until the end of the study (9/2023). Only pseudonymised data is used solely for scientific evaluation. The pseudonymisation key is saved separated from evaluated data in the study center in Heidelberg and can only be accessed by the study physicians. Third parties do not get any insight into original documents or data collected. It is deleted when the linkage between the two quantitative studies is completed.

Dissemination

Results of the different study phases are disseminated by publications in peer-reviewed scientific journals and by scientific conference contributions (e.g. abstracts, poster). Findings are further presented to the funder. The results could contribute to better understand, communicate and address financial impact in the future, e.g. by offering targeted support or considering financial effects in health technology assessments.

Project plan

Phase	Task	WP	(Anticipated) time schedule
1	Needs Assessment Patients	1	May 2021 – November 2021
	Needs Assessment social services, third-party payers and HTA institutions	2	October 2021
	Systematic literature review	3	October 2021
2	Questionnaire Piloting and Validation	4	December 2021 – February 2023
3	Piloting of a screening program for social services	5	February 2023 – July 2023
	Recommendations for the use of the measuring instrument	6	October 2023

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