PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A protocol for the development and validation of a patient-reported outcome tool to assess cancer-related financial toxicity in Italy
AUTHORS	Riva, Silvia; Bryce, Jane; De Lorenzo, Francesco; Del Campo, Laura; Di Maio, Massimo; Efficace, Fabio; Frontini, Luciano; Giannarelli, Diana; Gitto, Lara; Iannelli, Elisabetta; Jommi, Claudio; Montesarchio, Vincenzo; Traclò, Francesca; Vaccaro, Concetta Maria; Gallo, Ciro; Perrone, Francesco

VERSION 1 – REVIEW

REVIEWER	Jennifer Spencer, PhD Post-Doctoral Fellow, Harvard TH Chan School of Public Health, USA
REVIEW RETURNED	20-Jun-2019

GENERAL COMMENTS	This study seems well-designed and I look forward to seeing your results. Two minor comments: 1- In your discussion of your scoring procedure I would consider that you may have sub scores rather than a single composite measure. (This would reasonably be determined from both interviews and factor analysis). As discussed by Altice and others, financial toxicity is often described by both severity of mental effect (anxiety, low QoL) and as a product of actual behaviors (skipping medication, declining care, etc). In my experience, these two items can correlate but do not necessarily always move together. The writing is clear except in the section "Clinical Study within endpoint model 1". Please add clarification to the sentence “During this phase, the cooperation of major cooperative Italian groups will be of primary importance.”

REVIEWER	Louisa Gordon QIMR Berghofer Medical Research Institute Brisbane, Australia
REVIEW RETURNED	21-Jun-2019

GENERAL COMMENTS	Development and validation of a patient-reported outcome tool to assess cancer-related financial toxicity in Italy This article is a well-organised write-up of a study protocol to develop a new financial toxicity tool in Italy. The methods planned are reasonably clear and will follow recommended guidelines. The study as written though does have some gaps where further explanation or clarity would be useful for the reader. Details about how the authors are going to recruit patients for the various tasks are missing. Comments

	The paper would benefit from a thorough English-language proof read – there are some strange word choices which do not read well e.g., Line 13 of Abstract – financial 'shortcuts' when financial 'burden' is the actual meaning, use of word 'dramatic' line 14 (to delete), page 8 line 26 'frustrate' when 'lessen' is meant etc. There are several typos, missing words, problems with tenses and further improvements are required of the current version to reach a publishable standard of writing. There is no rationale given on the importance of developing this tool a) for cancer patients and b) for the Italian population. Why is cancer being singled out as the only disease relevant and why is the tool to be applicable for Italy only - as mentioned in the limitations. There is a useful financial toxicity tool already developed by US researchers, the COmprehensive Score for financial Toxicity (or COST). The authors do reference the early development study by de Souza in 2016 and align some of their methods to this but it has been psychometrically validated in a separate population (de Souza 2017), which is not discussed or referenced, and adapted to the Japanese population (with a universal health system) (Honda 2019) and used elsewhere – refs below: 1. de Souza JA, Yap BJ, Wroblewski K, et al: Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the Comprehensive Score for financial Toxicity (COST). Cancer 2017; 123:476-484, 11. 2. Honda K, Gyawali B, Ando M, et al: Prospective Survey of Financial Toxicity Measured by the Comprehensive Score for Financial Toxicity in Japanese Patients With Cancer. J Glob Oncol. 2019 May;5:1-8. 3. Huntington SF, Weiss BM, Vogl DT, et al: Financial toxicity in insured patients with multiple myeloma: A cross-sectional pilot study. Lancet Haematol 2015; 2:e408-e416. What differences to COST do the authors expect with their new tool? If the tool is only generalizable to Italy, why do they plan for external validation in other European populations and why only regional, couldn't it be used more broadly? Why couldn't they do a language translation of the COST for example? Introduction Page 6, lines 12-26 there seems to be an over-emphasis on US findings– but more relevant would be to summarise the studies from elsewhere in the world i.e expand on the last sentence Page 6 line 28. Page 6, lines 51-53 – I find it hard to agree with the statement. The COST does not mention co-payments for anti-cancer drugs (or any specific treatments or services) and many questions still apply to persons in a universal health system. Can the authors please justify this statement further? Page 7 – the whole page is devoted to their prior analyses which is lengthy. I can't see how this supports the rationale of the study specifically and has this work been published? If not, it should be referenced as unpublished. Methods Page 10 line 20 – caregivers are allowed to participate in the study but are these intended to be family members living in the same household, who would actually be close enough to the patient to understand what financial and social issues the patient has? I am wondering about caregivers outside the home e.g. for single patients living alone, and what role they have. This points to the general issue of defining 'financial difficulty' and other broad terms that will no doubt arise during interviews and focus groups.

	Page 11, line 50 – please clarify what ‘some degree’ means exactly? Page 14 line 27 – how are the 45 patients being recruited for this task, what are the details here and feasibility of this? Page 16 lines 15-20 – how are the 118 patients being recruited for this task, what are the details here and feasibility of this? Page 16 line 53, correlation with the EORTC QoL – the COST 2017 study could be reviewed and referenced here as the validation study looking at psychometric properties relating to convergent validity. How are the 220 patients being recruited for this task, what are the details here and feasibility of this? General – statistical analyses are not adequately detailed and could be expanded on.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jennifer Spencer, PhD
Institution and Country: Post-Doctoral Fellow, Harvard TH Chan School of Public Health, USA Please state any competing interests or state ‘None declared’: None Declared

Comment 1.
This study seems well-designed and I look forward to seeing your results.
Response 1.
Thank you very much.

Two minor comments:
Comment 2.
1- In your discussion of your scoring procedure I would consider that you may have sub scores rather than a single composite measure. (This would reasonably be determined from both interviews and factor analysis). As discussed by Altice and others, financial toxicity is often described by both severity of mental effect (anxiety, low QoL) and as a product of actual behaviors (skipping medication, declining care, etc). In my experience, these two items can correlate but do not necessarily always move together.
Response 2.
We thank Dr. Spencer for this comment. We completely agree. Actually, the protocol paragraph on Definition of scoring procedures is quite simple and short and refers to the fact that the Steering Committee will discuss opportunities on this point. However, the manuscript was not clear enough regarding the Steering Committee’s will to maintain some freedom in definitive decisions on scoring procedures. Your suggestion is supportive to this view. We have clarified this in the text.

Comment 3.
The writing is clear except in the section "Clinical Study within endpoint model 1". Please add clarification to the sentence “During this phase, the cooperation of major cooperative Italian groups will be of primary importance.”
Response 3.
We have added some clarification. Actually, one of the supporting bodies is FICOG (Federation of Italian Cooperative Oncology Groups) and we will look for their cooperation to improve feasibility in the phase where a high number of patients from a high number of centres will be required. Cooperative groups maybe a way to motivate participating centres.

Reviewer: 2
Reviewer Name: Louisa Gordon
Institution and Country:
QIMR Berghofer Medical Research Institute Brisbane, Australia Please state any competing interests or state 'None declared': None declared

Comment 1.
This article is a well-organised write-up of a study protocol to develop a new financial toxicity tool in Italy. The methods planned are reasonably clear and will follow recommended guidelines. The study as written though does have some gaps where further explanation or clarity would be useful for the reader. Details about how the authors are going to recruit patients for the various tasks are missing.
Response 1.
Thanks for this comment and hereunder we provide additional details as requested.

Comment 2.
The paper would benefit from a thorough English-language proof read – there are some strange word choices which do not read well e.g., Line 13 of Abstract – financial 'shortcuts' when financial 'burden' is the actual meaning [corrected], use of word 'dramatic' line 14 (to delete) [deleted], page 8 line 26 'frustrate' when 'lessen' is meant etc [substituted]. There are several typos, missing words, problems with tenses and further improvements are required of the current version to reach a publishable standard of writing.
Response 2.
Thanks for the suggested corrections. We have also done a language review.

Comment 3.
There is no rationale given on the importance of developing this tool a) for cancer patients and b) for the Italian population. Why is cancer being singled out as the only disease relevant and why is the tool to be applicable for Italy only - as mentioned in the limitations. There is a useful financial toxicity tool already developed by US researchers, the COmprehensive Score for financial Toxicity (or COST).
The authors do reference the early development study by de Souza in 2016 and align some of their methods to this but it has been psychometrically validated in a separate population (de Souza 2017), which is not discussed or referenced, and adapted to the Japanese population (with a universal health system) (Honda 2019) and used elsewhere – refs below:
1. de Souza JA, Yap BJ, Wroblewski K, et al: Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the Comprehensive Score for financial Toxicity (COST). Cancer 2017; 123:476-484, 11.
2. Honda K, Gyawali B, Ando M, et al: Prospective Survey of Financial Toxicity Measured by the Comprehensive Score for Financial Toxicity in Japanese Patients With Cancer. J Glob Oncol. 2019 May;5:1-8.
3. Huntington SF, Weiss BM, Vogl DT, et al: Financial toxicity in insured patients with multiple myeloma: A cross-sectional pilot study. Lancet Haematol 2015; 2:e408-e416.
What differences to COST do the authors expect with their new tool? If the tool is only generalizable to Italy, why do they plan for external validation in other European populations and why only regional, couldn't it be used more broadly? Why couldn't they do a language translation of the COST for example?
Response 3.
All of the comment 3 refers to the affinities between our proposed tool and the COST score. We appreciate the value of the COST instrument and we respect the excellent work done by the group of Dr. de Souza. We already cited and referenced two of the papers that the Reviewer is highlighting in her/his comment (the COST 2017 paper was actually reported as 2016 based on publication ahead of print, but the paper is the same). We did not reference just the Honda paper in JGO because it was

published after the submission of our manuscript. It has now been added. However, we had referenced the previous publication of the pilot study in eCancer Medical Science (ref. no.12 of the initial manuscript).
As for the rationale behind our study we think that differences in health care systems may deeply affect financial burden and their effect on patients' outcome (Rotter J, Spencer JC, Wheeler SB: Financial toxicity in advanced and metastatic cancer: Overburdened and underprepared. J Oncol Pract 15: e300-e307, 2019), and that a one-size-fits-all approach is not necessarily the best way to understand the phenomenon of financial toxicity outside of the US (Perrone F et al. Assessing financial toxicity in patients with cancer: moving away from a one-size-fits-all approach. J Oncol Pract. 2019 May 24:JOP1900200. doi: 10.1200/JOP.19.00200). It is good news that COST has been translated and used in Japan, but Japanese patients still pay out of pocket 30% of health care costs, as reported by Honda et al, even if additional protections against financial difficulties exist. Conversely, the Italian health system is strongly different from the US one since the government pays for 100% of health care costs; however, we found that some financial burden exists in Italy too and may affect QOL and survival of patients (Perrone F et al. The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy. Annals of oncology 2016;27(12):2224-29. doi: 10.1093/annonc/mdw433). Thus we hypothesized that a specific tool for the Italian context would be a more appropriate and sensitive approach to understand the magnitude and the determinants of the problem and to suggest possible strategies for fighting it. Quite differently from COST, indeed, we are also trying to perceive patients' reported experiences, not outcome alone (Coulter A. Measuring what matters to patients. BMJ 356:j816, 2017; Altice CK, Banegas MP, Tucker-Seeley RD, et al: Financial Hardships Experienced by Cancer Survivors: A Systematic Review. J Natl Cancer Inst, 2016). This is why we conservatively believe that the Italian instrument should be confidently applied in Italy only.
Although we agree that with health systems that share similarities (like US and Japan) there may be room for translations and use of single tools, we argue that some heterogeneity of tools is expected because of differences of social and cultural contexts, that should be more confidently dealt with using adequate and shared methods in the development process. Addressing these difference could be a future cooperation among European and non-European countries with assessment of the agreement between tools in a subsequent step.

Comment 4.
Introduction
Page 6, lines 12-26 there seems to be an over-emphasis on US findings– but more relevant would be to summarise the studies from elsewhere in the world i.e. expand on the last sentence Page 6 line 28.
Response 4.
The aim of the manuscript we are submitting is to report the approved study protocol, not to review and discuss the actual evidence worldwide on the matter. All the references reported in the last sentence have been published after our protocol had been submitted to ethical committees and we believe that further discussion of their content would be more reasonable when we will report our future findings.

Comment 5.
Page 6, lines 51-53 – I find it hard to agree with the statement. The COST does not mention copayments for anti-cancer drugs (or any specific treatments or services) and many questions still apply to persons in a universal health system. Can the authors please justify this statement further?
Response 5.
We understand that the statement might be too strong even though we have explained our position above .. In any case, we have changed the statement to be less restrictive: "However, this questionnaire might not be sensitive to relevant issues in health systems where co-payment for anticancer drugs is not required."

Comment 6.
Page 7 – the whole page is devoted to their prior analyses which is lengthy. I can't see how this supports the rationale of the study specifically and has this work been published? If not, it should be referenced as unpublished.
Response 6.
We thank the reviewer for this suggestion and have now further clarified this aspect in the revised version. Indeed, we note that we started the development of our financial tool mainly because of our previous findings (Perrone F et al. The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy. Annals of oncology 2016;27(12):2224-29. doi: 10.1093/annonc/mdw433). That is why we extensively explained these data in the protocol introduction and we believe that these data strongly support the rationale of the project. To fully address this remark, we have now made some changes and shortened a bit this paragraph. We also understand that the position of the citation (after the first statement of the paragraph only) could be confusing and we have recalled it at the end of the paragraph.

Comment 7.
Methods
Page 10 line 20 – caregivers are allowed to participate in the study but are these intended to be family members living in the same household, who would actually be close enough to the patient to understand what financial and social issues the patient has? I am wondering about caregivers outside the home e.g. for single patients living alone, and what role they have. This points to the general issue of defining 'financial difficulty' and other broad terms that will no doubt arise during interviews and focus groups.
Response 7.
We thank the Reviewer for this comment. We did not select a priori the type of caregiver but details are collected in the case-report forms and will be matter of attention in the analysis of focus groups.

Comment 8.
Page 11, line 50 – please clarify what 'some degree' means exactly?
Response 8.
Any response score ≥ 2 (the scale is from 1 to 4 with 1 representing no problem at all). Corrected in the text.

Comment 9.
Page 14 line 27 – how are the 45 patients being recruited for this task, what are the details here and feasibility of this?
Response 9.
Sorry for lack of clarity on this point. The same inclusion/exclusion criteria are applied for all the phases involving patients in this protocol. They are reported in the "Inclusion/exclusion criteria" paragraph of the
METHODS AND ANALYSIS section. We have added a statement to clarify this. Feasibility is not considered a problem because the three Institutions involved in this phase are all cancer centres with a high volume of patients.

Comment 10.
Page 16 lines 15-20 – how are the 118 patients being recruited for this task, what are the details here and feasibility of this?
Response 10.
Sorry for lack of clarity on this point. The same inclusion/exclusion criteria are applied for all the phases involving patients in this protocol. They are reported in the "Inclusion/exclusion criteria" paragraph of the

METHODS AND ANALYSIS section. We have added a statement to clarify this.
Feasibility is not considered a problem because the number of participating Institutions will be increased up to 10-12 centres dedicated to cancer treatment, distributed across Italy to warrant a uniform geographic distribution. The same number of patients (around 10-12 patients) will be enrolled at each centre.

Comment 11.
Page 16 line 53, correlation with the EORTC QoL – the COST 2017 study could be reviewed and referenced here as the validation study looking at psychometric properties relating to convergent validity.
Response 11.
We already cited the COST 2017 study in this paragraph as an example of this kind of analysis. We also reported details of its findings.

Comment 12.
How are the 220 patients being recruited for this task, what are the details here and feasibility of this?
Response 12.
Sorry for lack of clarity on this point. The same inclusion/exclusion criteria are applied for all the phases involving patients in this protocol. They are reported in the "Inclusion/exclusion criteria" paragraph of the
METHODS AND ANALYSIS section. We have added a statement to clarify this. Feasibility is not considered a problem because the number of participating Institutions will be increased thanks to the collaboration with several institutions/collaborative groups participating to FICOG (Federation of Italian Collaborative Oncology Groups). Such centres are dedicated to cancer treatment, and we will carefully control a uniform geographic distribution.

Comment 13.
General – statistical analyses are not adequately detailed and could be expanded on.
Response 13.
We reported information on statistical analysis as they are stated in the approved protocol. A detailed statistical analysis plan will be developed as an additional document to the study protocol before such analysis are done and will be submitted with future reporting of study results. In any case, we will rigorously follow the statistical procedures as described by the ISPOR PRO insutrument guidelines.

VERSION 2 – REVIEW

REVIEWER	Jennifer Spencer Harvard TH Chan School of Public Health Boston, MA USA
REVIEW RETURNED	08-Aug-2019

GENERAL COMMENTS	The authors have addressed my concerns adequately.