



## Rationale and study design: A randomized controlled trial of early palliative care in newly diagnosed cancer patients in Addis Ababa, Ethiopia

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### ABSTRACT

Patient-reported outcomes and economic aspects of Palliative Care (PC) provision in low-income countries (LIC) are under-studied. Demonstrating the economic value of PC is key to sustainability and guiding health care policy. Our preliminary data in Ethiopia demonstrated a widespread need for PC, poor access to it, and high out of pocket payments (OOP). We suspect that in this and other LIC, PC may function not only to reduce suffering but also as a poverty reduction strategy.

We are conducting a randomized controlled trial of standard Oncology care versus standard Oncology care plus PC in newly diagnosed cancer patients in Addis Ababa. Ninety-seven adults presenting to Oncology Clinic will be randomized in a 1:1 ratio. Subjects receiving PC will meet with a PC provider at time of enrollment and at follow up visits in their homes. All subjects will be assessed via questionnaire at enrollment and follow-up Oncology visits at  $8 \pm 4$  and  $12 \pm 4$  weeks. A cost-consequence analysis will be performed, to include: patient-reported OOP and healthcare utilization, the latter to be assessed through chart adjudication. Outcomes will include change in African Palliative Care Association Palliative Outcome Score, changes in OOP and healthcare utilization.

We hypothesize that the cost of home-based PC will be offset by improvements in patient-reported outcomes, decreased OOP and healthcare utilization, rendering PC cost-effective in this LIC. These findings may lead to widespread dissemination of an effective, sustainable and cost-saving public PC delivery strategy that would improve the quality of life and death for millions of people.

*Trial registration:* Clinicaltrials.gov [NCT03712436](https://clinicaltrials.gov/ct2/show/study/NCT03712436).

### 1. Introduction

With the rise in non-communicable diseases (NCD), an epidemiological transition is underway: globally, people are living longer with incurable disease [1]. As a result, there is a great need to expand health care delivery for all stages of chronic illness, including palliative care. Of the 61 million people globally in need of palliative care, just 14% receive it, largely in high-income countries [2–4]. Within fragile health systems that lack palliative care, incurable illness is of-

ten marked by pain and suffering, as well as devastating costs of seeking medical care [5]. Universal Health Coverage calls for quality healthcare for all, from preventative to palliative, without financial burden, yet globally, millions of people are impoverished by the costs of seeking medical care [6–8].

Out of pocket payments (OOP) refer to payments made directly by individuals to healthcare providers, at the point of service. In settings where healthcare providers are inadequately paid, OOPs provide a major source of revenue, while simultaneously absorbing the financial

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resources of a patient, thus increasing the incidence of catastrophic health expenditures (CHE).<sup>5</sup> CHE is defined as out-of-pocket spending for healthcare that exceeds a certain percentage of household income, with the consequence that households suffer the burden of disease [9].

In countries that rely on OOPs to finance their healthcare system, the financial burden of medical care is borne by patients and families, often at the expense of essentials such as food and children's education. High OOP also may discourage patients from seeking medical care, or be a factor in delaying the seeking of care [10]. In Africa, the risk of CHE is increased in the following vulnerable groups: low socioeconomic status, rural residence, not having health insurance, long inpatient days and having a chronic disease [11,12].

We previously reported the results of a palliative care needs assessment in Ethiopia, which demonstrated a great need for palliative care provision, particularly in the Oncology population, and the tremendous costs of illness, largely in the form of OOP, that are absorbed by patients with incurable disease and their families, often with little knowledge of prognosis. In order to cope, children were pulled from school as fees became unaffordable, and major assets were sold, including livestock, land and wedding gold [13].

Other results included high pain scores coupled with inadequate access to analgesic medications and high OOPs for incurable illness, often with little to no knowledge of prognosis.<sup>11</sup> We concluded that the need to formally implement public palliative care interventions is an urgent priority, and hypothesized that palliative care may function as a poverty reduction strategy in this and other low income countries (LIC) through a decrease in OOP and healthcare utilization [14].

We recently published a systematic review of the cost-effectiveness of global palliative care, the results of which highlighted the need for more, and robust, cost-effectiveness analyses in LIC [15]. Demonstrating the economic value of palliative care in LIC is key to sustainability and crucial for guiding health care policy [16,17].

## 2. Methods and study design

### 2.1. Overview

There are two overarching specific aims in this project. The first is to study the effect of initiation of palliative care on patient-reported palliative outcome measures as assessed by the African Palliative Care Association Palliative Outcome Scale (APCA POS) [18] and Needs Near End of Life Screening Tool (NEST 13). [19] We expect improved quality of life and decreased symptom burden, as measured by a significant decrease in both scores in those patients receiving palliative care.

The second aim is to perform a Cost Consequence Analysis (CCA), a type of economic analysis that looks at disaggregated costs and consequences and is thought to be a specifically useful tool for assessing complex interventions with multiple effects, and interventions with a variety of non-health benefits, such as palliative care [20,21]. The CCA will evaluate the following: (1) the cost of delivery of home-based palliative care over the study duration, (2) patient-reported OOP for medical care, (3) hospital-generated costs and healthcare utilization in those patients receiving palliative care, (4) patient-reported outcomes including change in APCA POS and NEST scores, and (5) survival.

A societal perspective will be considered, and comprised of three key perspectives: the patient and family as fully one third of medical expenses in Ethiopia are OOP borne by the patient and family [22,23], Hospice Ethiopia as the deliverer of Palliative Care, and the government, as they health system payer (see Fig. 1: Study Flow).

### 2.2. Study population

A sample size of 47 per group is needed to provide 80% power to detect of difference of 3 at week 8 on the APCA POS score at a 2-sided significance level of 0.05 and attrition of 25%, assuming standard de-

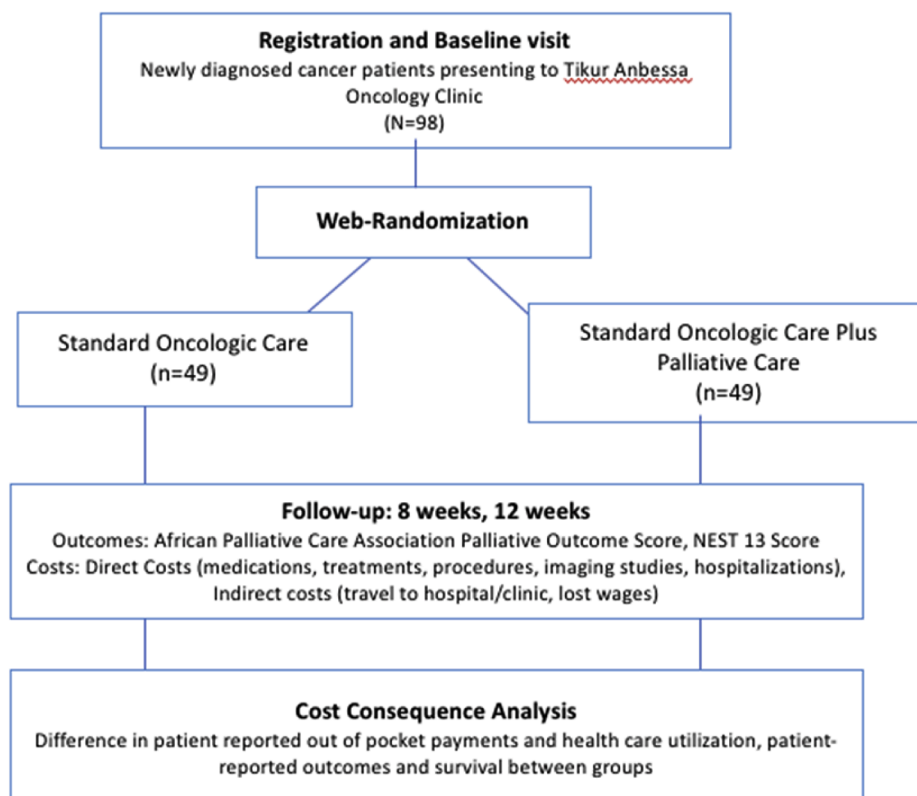


Fig. 1. Study flow.

viation of 4.5 for both groups. Patients who have received a diagnosis of cancer within the prior 4 weeks will be invited by their Oncologist to participate in the study. Patients with any newly diagnosed cancer who are ambulatory and able to respond verbally to questions, are eligible for inclusion. Patients with diagnoses made more than 4 weeks ago, who are non-ambulatory, or are already receiving palliative care, are ineligible to participate in the study. All eligible patients will be approached for enrollment. No other recruitment will be done. Subjects will be randomized via a web randomization tool in a 1:1 ratio to one of the two study arms. All subjects will provide written informed consent. All subjects will receive standard oncologic care throughout the study period unless they or their family decide that standard oncologic care no longer aligns with their goals of care, in which case they will be withdrawn from the study however offered ongoing Palliative Care through Hospice Ethiopia, should they desire it.

### 2.3. Intervention and comparator

Subjects randomized to early palliative care will meet with a Palliative Care provider at time of enrollment and at follow up visits in their homes, as frequently as deemed indicated by Hospice Ethiopia staff, and according to Hospice Ethiopia guidelines for the practice of Palliative Care in this setting. Palliative care providers are Ethiopian physicians and nurses trained in palliative care practices. All subjects in both study arms will be assessed via questionnaire at enrollment and at follow up visits in Oncology clinic. (Fig. 2, Supplementary file). No data will be collected during home hospice visits. Follow-up will occur at 8 weeks (or at an outpatient clinic visit within 4 weeks before or after this time point) and at three months.

### 2.4. Outcomes

To evaluate the impact of initiation of Palliative Care in this population, we will measure the proportion of subjects in both study arms with improved quality of life, as measured by a decrease in APCA POS or NEST 13 scores (Table 1: Quality of Life Outcomes). We will also compare OOP for medical care, healthcare utilization and survival.

### 2.5. OOP and healthcare utilization

To estimate healthcare utilization, hospital charts of subjects in both study arms will be adjudicated at study end for costs generated by the clinic and hospital (Table 2). Chart adjudication will be performed by native Amharic speakers with a degree of Registered Nurse

or Medical Doctor, and experience working in an Oncology population. Economic results will be reported in 2019 USD.

### 2.6. Intervention costs

The cost of delivering home-based palliative care is estimated at 265 Ethiopian birr/visit (9.25 USD), which includes the time of the healthcare worker, gas, and medicines. The estimate does not include overhead costs of running Hospice Ethiopia (building rental, janitorial fees, vehicle) as this is already in place.

### 2.7. Ancillary study: novel biomarker

The neutrophil to lymphocyte ratio (NLR) is being evaluated as a predictor of longevity and response to chemotherapeutics. This simple calculation, available from a widely available and basic blood test that is already drawn at the time of presentation to Oncology clinic, may provide powerful information to help guide Oncologists in their discussions with patients about the risks, benefits and costs of pursuing treatment. It is particularly important in resource limited settings, and in settings with poor health infrastructure where patients and families absorb the costs of illness. Thus far, it has only been studied in northern populations [24,25]. The NLR will be calculated at study end, during the hospital chart adjudication.

## 3. Discussion

We are publishing our study protocol in order to increase the transparency of the economic evaluation within our clinical trial, and to provide a template for conducting a CCA of palliative care in a low resource setting. The protocol follows international guidelines for economic evaluations [26,27]. Economic evaluations from high income countries have shown that palliative care is cost-effective [28–34]. A dearth of similar analyses in low resource settings has produced a gap in hard health economic data on palliative care delivery in low income settings [13]. Our aim in providing this template is to encourage other CCA of palliative care in similar settings, thus generating the data to support the funding of widespread, public palliative care services in low resource settings.

This manuscript describes the protocol for an economic evaluation of a randomized controlled trial of Palliative Care in newly diagnosed cancer patients in Addis Ababa, Ethiopia. There are some notable strengths of this study. First, the study design is a randomized controlled trial of early palliative care in a low resource setting. As such, it is the first of its kind on the continent of Africa and is responding to

### Subject Process

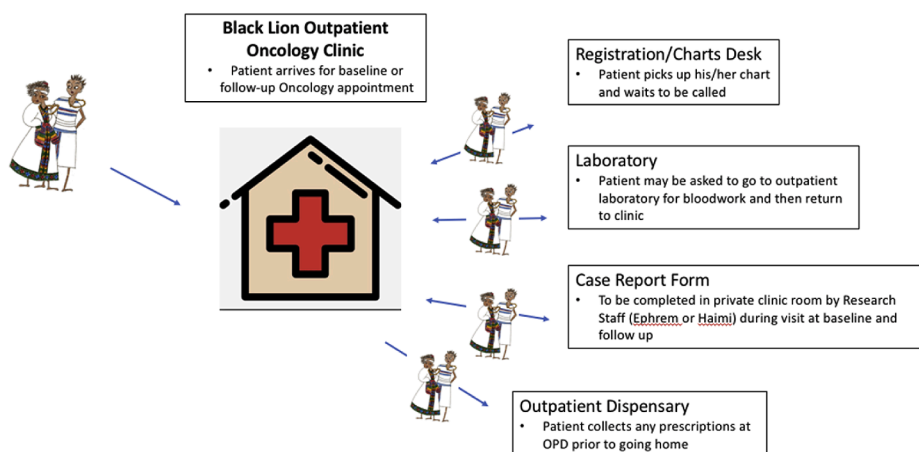


Fig. 2. Subject process.

**Table 1**  
Quality of life outcomes.

|  | Outcome  | Source                     | Time of collection         |
|--|--|----------------------------|----------------------------|
| APCA POS (scale of 0–5)                              | Pain   | CRF                        | Baseline, Follow-up visits |
|  | Other symptoms                                       | CRF                        | Baseline, Follow-up visits |
|  | Worry  | CRF                        | Baseline, Follow-up visits |
|  | Able to share feelings                               | CRF                        | Baseline, Follow-up visits |
|  | Life feels worthwhile                                | CRF                        | Baseline, Follow-up visits |
|  | Sense of peace                                       | CRF                        | Baseline, Follow-up visits |
|  | Able to plan for future                              | CRF                        | Baseline, Follow-up visits |
|  | Information given to family                          | CRF                        | Baseline, Follow-up visits |
|  | Family able to care for patient                      | CRF                        | Baseline, Follow-up visits |
|  | Family worry   | CRF                        | Baseline, Follow-up visits |
| NEST 13 (scale 0–10)                                 | Financial hardship                                   | CRF                        | Baseline, Follow-up visits |
|  | Trouble accessing care                               | CRF                        | Baseline, Follow-up visits |
|  | Help needed with ADLs                                | CRF                        | Baseline, Follow-up visits |
|  | Illness seems senseless/meaningless                  | CRF                        | Baseline, Follow-up visits |
|  | Suffering from physical symptoms                     | CRF                        | Baseline, Follow-up visits |
|  | Confusion/anxiety/depression                         | CRF                        | Baseline, Follow-up visits |
|  | Have someone to confide in                           | CRF                        | Baseline, Follow-up visits |
|  | Religion/spirituality contribute to sense of purpose | CRF                        | Baseline, Follow-up visits |
|  | Settled relationships with family/friends            | CRF                        | Baseline, Follow-up visits |
|  | Special sense of purpose                             | CRF                        | Baseline, Follow-up visits |
|  | Worry about the costs of care                        | CRF                        | Baseline, Follow-up visits |
|  | Money spent in last month on medical care            | CRF                        | Baseline, Follow-up visits |
|  | Caretaker lost wages                                 | CRF                        | Baseline, Follow-up visits |
| Sale of personal belongings to pay for medical care? | CRF  | Baseline, Follow-up visits |                            |

an urgent need. It is further strengthened by the expertise of local Palliative Care providers at Hospice Ethiopia, and highly motivated healthcare providers at Tikur Anbessa Oncology Clinic, both of whom have supported the project and its goals from the earliest stages of planning.

### 3.1. Limitations

For economic evaluations within randomized controlled trials, it is important to identify sources of bias that might undermine validity of results. This includes selection or recruitment bias and process or protocol deviation [35,36]. The study does have some limitations. The pragmatic nature of the trial meant that during a morphine stock out, study start was delayed, and then the protocol was modified to reflect a national absence of liquid oral morphine, replaced instead with tablets. Our standard protocol, involving liquid oral morphine, resumed as soon as it was available. In addition, there is a limited amount of available chemotherapeutics, and thus preference is to those patients thought most likely to respond to chemotherapeutics rather than all comers. This represents an important limitation to the

**Table 2**  
Cost measures.

|                          | Type of cost   | Source                      | Timing of collection          | Units             |
|--------------------------|--|-----------------------------|-------------------------------|-------------------|
| Patient-reported Costs   | Out of Pocket payments for all medical costs in the last month | CRF                         | Baseline and follow-up visits | Ethiopian birr    |
|                          | Worried about the costs of care                                | CRF                         | Baseline and follow-up visits | Y/N               |
|                          | Time caretaker has taken off of work                           | CRF                         | Baseline and follow-up visits | Ethiopian birr    |
|                          | Lost wages   | CRF                         | Baseline and follow-up visits | Ethiopian birr    |
| Hospital-generated costs | Sale of personal items to cover medical costs                  | CRF                         | Baseline and follow-up visits | Y/N and free text |
|                          | Metastatic work up   | Hospital chart adjudication | Study end                     | Ethiopian birr    |
|                          | Diagnostic imaging (CT/Xray)                                   | Hospital chart adjudication | Study end                     | Ethiopian birr    |
|                          | Chemotherapeutics  | Hospital chart adjudication | Study end                     | Ethiopian birr    |
|                          | Non-opioid pain medications                                    | Hospital chart adjudication | Study end                     | Ethiopian birr    |
|                          | Opioid analgesia Medical procedures                            | Hospital chart adjudication | Study end                     | Ethiopian birr    |
|                          | Hospitalizations   | Hospital chart adjudication | Study end                     | Ethiopian birr    |

study. We have tried to mitigate this with a randomized controlled trial study design—as our Oncologist is blinded to study group, he is unaware which of his patients are also receiving palliative care and is thus offering the same care to patients in both study arms. This should minimize bias between groups. The study is not designed to control or account for outcome differences in particular cancers at certain stages.

We included patients only from Addis Ababa in this study, for ease of follow up. As Tikur Anbessa is a tertiary hospital, patients travel great distances for care, and then often return to their homes, which would have made follow up near-impossible. Another limitation is the relatively short follow-up period. The main risk of this short follow up is that our study will not detect a significant effect of palliative care due to the short follow up period. The reason this follow up window was selected is due to the very late presentations for cancer and thus short survival window in this population, and needing to find equipoise between minimizing loss to follow up which would likely occur with a longer follow up window, with following patients long enough to detect a difference between groups. There is a risk that the short follow up period may minimize differences between groups or incorrectly fail to show a difference (false negative result). These aspects of our study may introduce some selection bias into our study and do limit the applicability to other populations.

The reliance on patient-reported OOP for medical costs may impact the validity of study results. It also may be difficult in a subsistence economy for subjects to generate number-based responses. However, we have used faces when possible (for patient-reported outcomes) also asked about the sale of major assets, which in our previ-

ous work in this setting, proved to be an effective way of ascertaining the degree of financial stress placed on a family during a time of illness.

In conclusion, we hypothesize that the cost of delivery of home-based palliative care will be offset by improvements in patient-reported outcomes, a decrease in OOP and healthcare utilization, thus rendering the delivery of palliative care cost-effective in this low-resource setting. These ground-breaking results will be highly relevant to patients and families struggling with both poverty and high medical costs, and to healthcare workers and policy makers working to improve palliative care delivery for millions of people with incurable disease.

## Ethics

Institutional Review Boards at Yale University School of Medicine and Tikur Anbessa College of Health Sciences approved the study. All patients provided written informed consent prior to participating in this study.

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## Declaration of competing interest

All authors declare that they have no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2020.100564>.

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