

# Healthcare Cost-Effectiveness Analysis for Older Patients: Using Cataract Surgery and Breast Cancer Treatment Data

## Chapter 6

### Current Issues and Future Work

Arash Naeim, M.D.

Geriatric-Oncology Fellow

RAND-UCLA Doctoral Fellow in Public Policy

Division of Hematology-Oncology

Department of Medicine

University of California, Los Angeles

Los Angeles, California

## Introduction

Patients, physicians, nurses, insurers, and policymakers would probably all agree that providing high quality cost-effective medical care to older patients is essential. Differences in opinion may exist though on how to define “high quality” and the standards and methods used to assess cost-effectiveness. This dissertation has highlighted several aspects of performing cost-effectiveness analysis using: (a) a randomized control trial of cataract surgery and (b) modeling using data derived from meta-analyses of trials with mainly patients under 70 years of age. Each analyses demonstrated inherent limitations.

Although randomized control trials are considered the “gold standard” for evidence-based data, there may be problems with adequate accrual (statistical power), selection bias, and precise measurement of outcomes using generic instruments (such as the Health Utilities Index Mark3 in the randomized cataract surgery trial). Furthermore, randomized clinical trials are expensive and slow. On the other hand, any modeling exercise, even though relatively inexpensive, relies on a set of assumptions, the validity of which can always be challenged.

Several issues need to be resolved in order to determine optimal treatment choices and pathways for older patients. These issues include the following: (1) improving clinical trial recruitment of a representative population of older patients; (2) developing outcome measurement instruments reliable and valid in an older population; (3) defining approaches to communicate uncertainty in treatment outcome to patients; (4) soliciting treatment preferences from older patients, (5) creating a decision aid that incorporates the best available clinical evidence with patient preferences in order to individualize treatment, and (6) collecting functional status\*, comorbidity, patient preference, treatment intensity, and outcome data (disease progression, mortality, and quality of life\*\*) prospectively to further define the complex interactions that shape the healthcare treatment of older patients. Future work on these issues may lay the foundation required to overcome many of the limitations described in this dissertation.

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\* Functional Status refers to the ability of an individual to perform required daily tasks at home and at work. It reflects the level of physical strength, mobility, and energy level of an individual.

\*\* Quality of Life is a subjective measure of one’s overall enjoyment of life. It includes some of the components of functioning, similar to Functional Status, but also includes other physical (pain, nausea,...), social, and emotional components. Therefore, even though an individual may objectively have a poor functional status, they may rate their overall quality of life high, or vice versa.

## Performing Clinical Trials on Older Patients

Clinical trial recruitment played a central issue in both the cataract surgery trial and the breast cancer modeling analysis. In the randomized trial of cataract surgery, the recruitment, enrollment, and follow-up of older patients was very labor intensive. These obstacles limited the number of patients in the trial. This resulted in adequate power<sup>φ</sup> to measure significant changes in visual functioning but not enough power to measure changes in overall utility (although the sensitivity of the instrument to small changes plays a role as well). The lack of recruitment and enrollment of older patients in clinical trials was also a feature of most breast cancer trials [1] looking at adjuvant treatment. However, the critical contributing factor in these trials were the protocol exclusion criteria in many trials limiting participation to: (a) those under 70, (b) with good performance status, and (c) minimal comorbidities.

Can the information in the cataract and breast cancer clinical trials be extended to older patients in the community? In the cataract surgery trial the enrollment of only cognitively and hearing intact patients was required in order to complete the outcome surveys. Even though the patients were all over 65, there was probably selection bias. The data from breast cancer trials is even more suspect since older patients represented such a small percentage of the participants, and those that were enrolled probably represented the healthiest subgroup.

Several possibilities exist to improve clinical trial data for older patients. A more stringent application of the FDA guidelines for the study of drugs likely to be used in the elderly would be a good start. Two approaches are available for improving the implementation of these guidelines. First, there could be a requirement placed that all phases of clinical trials should have samples that reflect the percentage of older patients with the disease entity being studied. Alternatively, there could be a requirement that Phase IV clinical studies be performed specifically to determine treatment response in older patients. This secondary approach though suffers from the lack of data on treatment safety and toxicity specific to older patients derived from earlier phases of clinical trials.

Including older patients, who on aggregate have more comorbidities and functional limitations, requires a reformulation of clinical trial protocols. If only the healthiest of older patients

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<sup>φ</sup> Power is defined as the ability of a study to find true differences of between two groups or arms (ex control and treatment group). It is determined by the sample size and the “effect size”, the standardized difference between the two groups at a specific confidence level (95%). Power=0.8,  $\alpha=0.05$ .

are enrolled in clinical trials, then healthcare providers will still be in a quandary as to how to treat the average patient presenting in their clinics. On the other hand, including a frail subgroup would require dose and interval adjustments of many drugs in clinical trials. Perhaps companion protocols for clinical trials designed specifically to address these issues would be helpful. The International Conference on Harmonization of Technical Requirements (ICH) published a guideline for industry for Registration of Pharmaceuticals for Human Use on studies in support of older populations. This document highlighted the importance of including patients over the age of 75 and avoiding unnecessary exclusion of patients with concomitant illnesses [2]. Specifically highlighted was the need to recognize pharmacokinetic differences between younger and older patients, often related to impairment in renal or hepatic function or to drug-drug interactions [2].

Once older patients are appropriately represented in clinical trials rather than excluded, focus can be shifted in developing better strategies for patient recruitment. Further research needs to focus on how to better integrate primary care physicians and geriatricians in the clinical trial process. Educating community physicians on the existence of trials, their criteria, and the pros and cons of a trial for an older patient is essential. Since so many clinical trials are performed, the task may initially seem overwhelming. However, creating user-friendly databases that physicians can access via the Internet or on a Compact Disk that focus specifically on trials for which older patients are eligible would be of great help. These databases may be a resource not only for healthcare providers but also older patients and their families seeking cutting-edge treatment for their illness.

Finally, a concerted effort must be made to facilitate an older patient's continued participation in a trial once they have agreed to participate. Clinical trials often require more follow-up visits, more paperwork, and more lab tests. Older patients who live alone and have difficulty with transportation are a great risk for either loss to follow-up or poor compliance to the clinical trial regimen. A multidisciplinary approach to patient care utilizing the additional services of a social worker, physician and occupational therapist, pharmacist, and nutritionist would greatly supplement the standard care provided older patients on clinical trials. Considering that one in five individuals will be over the age of 65 within the next several decades, it is important that researchers and policymakers view older patients not as an obstacle that needs to be overcome but more an untapped exciting opportunity to provide more generalizable clinical trial data.

## **Outcome Measurement Instruments in Older Populations**

There is a plethora of health-related quality of life (HRQOL) measures currently available for use. In the cataract surgery trial, the key outcome measure for the cost-effectiveness analysis was the Health Utilities Index, Mark 3, HUI3. The HUI3 is a generic instrument. One concern with selecting a generic instrument measuring overall health was its sensitivity in measuring changes related to just vision. Alternatively a condition-specific (vision) measure might have been more sensitive to visual changes. The decision to choose either a generic or condition-specific HRQOL is controversial [3-6]. In older patients, who have many competing illnesses, there is a strong argument for using generic HRQOL measures since the goal is to determine the benefit of an intervention in the context of overall health. Some researchers argue that the standard should be to include both generic and disease-specific instruments [7], while others argue there is no clear guideline on deciding how to use the results from two different instruments [1].

More importantly, it is not clear if HRQOL measured in a clinical trial population is representative for a non-clinical trials population. One interesting study focused on the HRQOL in two cohorts of patients with human immunodeficiency virus (HIV) disease: (a) multi-center AIDS Clinical Group Trials in which most subjects are white, privately insured, and high-income (n = 1,907); and b) a study of ethnically diverse, low-income patients recruited from public clinics (n = 205) [8]. HRQOL scores were significantly lower in the non-trial sample ( $P < 0.001$ ) by about one standard deviation, even after direct adjustment for clinical and demographic characteristics [8], raising concerns about generalization of HRQOL results from clinical trials.

The psychometric properties of these instruments are usually estimated in patient and population settings where older individuals are under-represented. An argument can be made that these instruments should be assessed in an older population. Additionally, the use of aggregate quality of life data and preference weights from younger patients may be biased. For example, the modeling of adjuvant therapy of breast cancer used quality of life weights derived from clinical trials, which excluded patients over the age of 70. Aggregate values may not be the best approach to adjusting for quality of life even if, derived in an older population (see preference solicitation discussion below).

## **Communicating Risk and Benefit with Uncertainty**

Communicating risk and benefit to patients when there are insufficient data or too many complicating variables is an understudied area. The communication of risk and benefit is essential with both cataract surgery and adjuvant therapy for breast cancer. Previous studies using the Cataract Surgery Index, CSI, have shown that the probability of benefiting from surgery can be predicted. The manner in which probabilities should be expressed to patients and how they are adjusted for other factors, such as competing illnesses or underlying functional status, is unclear. These issues are magnified when discussing adjuvant breast cancer for an older patient where there are several complex sequential steps. First, there needs to be extension of the benefits and side effects of treatment from clinical trials in younger patients to older patients. Next, a baseline life expectancy needs to be derived for the patient without treatment. This baseline is derived from aggregate life table data from a very heterogeneous older population based on chronological age. There is no accepted method of adapting life expectancy for individual levels of comorbidity and functional status to derive a true individualized physiologic life expectancy. This baseline then needs to be adjusted for additional mortality risk from the acute disease. Finally the uncertain benefit and baseline life expectancy need to be combined to determine the quality-adjusted life years gained with treatment.

Communicating the uncertainty behind this entire process to an older patient may be confusing. One might argue that uncertainty should not be communicated at all, just a physician's best recommendation. However, given that informed consent to treatment is a cornerstone in medicine, and adequate informed consent requires a thorough discussion of risk and benefits, the discussion of uncertainty seems a prerequisite.

Most of the sparse literature on communicating uncertainty comes from cancer screening and treatment. In cancer screening, testing for a gene or protein can help demonstrate that someone has a higher probability for the development of a future cancer. Communicating cancer risk information from this type of testing is germane to a number of health professions including physicians, geneticists, genetic counselors, psychologists, nurses, health educators and social workers [9]. Some recent work has focused on techniques in communicating risk and benefits, but none of these studies have specifically focused on an older population nor have they incorporated the communication of degrees of uncertainty [10-13]

## **Preference Solicitation in Older Patients**

Some have argued strongly that preference measures may not be appropriate for older patients. Threats to validity of these instruments include: construct under-representation and construct-irrelevant variance [14]. Construct under-representation occurs when a stimulus presented to a judge fails to fully represent the depth and complexity of information required in actual judgments [14]. Construct-irrelevant variation occurs when factors irrelevant to preferences influence measurements of utilities. Among several factors that cause construct-irrelevant variation are cognitive abilities, calculation skills, emotions and prejudices, and the elicitation procedure [14]. Cognitive abilities and the ability to perform numerical calculations are often diminished in older patients. Furthermore, commonly used elicitation methods (visual-analog scales, time tradeoff, and standard gamble) capture different preference facets (desirableness of states, time preferences, and risk attitude) to different degrees [14].

Although there are reports of patient preferences for different types of cancer treatments [15], little work has been performed on the preferences of older cancer patients. Unfortunately, communication with older patients regarding treatment options and benefits is often time consuming for oncologists. As a result, patient preferences are often not incorporated adequately into the decision making process [16]. Previous research has shown that with methods adapted for their limitations, health preferences can be successfully elicited in patients over the age 80, but these preferences varied greatly depending on baseline health. Preference solicitation in the elderly must consider how patients feel about health in the absence of the disease being studied (i.e. how bothered patients are about their specific comorbidities) [17].

## **Decision Aids and Individualizing Treatment**

Although eliciting preferences can be challenging, several studies have shown that incorporating individual preferences into decisions may help with physician and patient education, empower patients, and help establish treatment recommendations [18-20]. A study of 60 early-stage

breast cancer patients showed that patient participation in deciding cancer treatment empowered many patients and promoted responsibility for their own care [21]. Since the amount of acceptable risk or tolerance for uncertainty is likely to be heterogeneous in an older population of patients, models that allow incorporation of individual preferences may be more representative than those that use general population weights [22].

The use of preferences and decision analysis has been used successfully in the treatment of patients with T3 laryngeal lesions, prophylactic oophorectomy, and atrial fibrillation[23, 24] [25] [26]. Tools incorporating patient preferences have lead to better-informed patients, better care, and better health outcomes from the patient's point of view. In addition to helping tailor care to individuals, these decision tools will help link evidence-based medicine into clinical practices and may improve the quality of care [27].

Recently, computer programs have been developed that use decision models and automatically create evidence-based guidelines and recommendations and that can be individually tailored and updated. An example has been a software system called ALCHEMIST that utilizes decision models to create evidence-based guidelines. This tool has been used with success in studying the need for implantable cardioverter defibrillators (ICD) and BRCA breast cancer mutation testing in women. The study showed that such a web-based system could easily incorporate individual preferences, weighting for relevant health states, and create patient-specific recommendations that result in an increase in quality-adjusted life expectancy [28].

## **Database Development**

The fact that older patients tend to have additional comorbidity and functional limitations creates additional challenges in determining if high quality of care is provided. Treatment selection, under-treatment and over-treatment, is related not only to important factors such as disease stage, comorbidity and functional status, but also less justified factors such as age, gender, and race. Breast cancer is a perfect example since older patients are often under-treated in terms of surgery, radiation, and hormone therapy, and sometimes over-treated when it comes to chemotherapy [29] [30, 31]. Most of the studies trying to separate the impact of these multiple factors in older patients have been retrospective.

Prospective population-based study looking at the factors that determine treatment of older patients is needed. For example in cancer, it would be very valuable to look at treatment selection and chemotherapy dosing in older patients. Older patients are often not offered chemotherapy, and when given, doses are often reduced. To determine whether dose-reductions are justified or these reflect ageism, one would need to collect information on a wide range of confounders including functional status, comorbidities, physiologic (kidney and liver) function, and patient preferences. Furthermore, it would be important to determine if the treatment variation that occurs among older patients has an effect on outcomes (quality of life, disease progression, hospitalizations, and mortality). This information would be essential in confirming or refuting many of the assumptions used in the modeling of benefits from adjuvant chemotherapy in older breast cancer patients.

These types of studies can be helpful in the development of interventions to improve the care of older patients. Ideally a database with these important variables would be national project or at least representing a large collaborative group of institutions. Unfortunately, a project of this magnitude is costly and may have to begin at local institutions where research on the care of older patients is a priority.

## **Conclusion**

Health services research, particularly cost-effectiveness analysis, on older patients will play a critical role in the next several decades. As the population of older individuals grows, policymakers will need to make difficult resource decisions in order to provide for this community. More clinical trials need to be designed to incorporate older patients and reflect the characteristics of general community. The lack of information on treatment benefit for older patients leads to uncertainty, which makes communication of treatment benefits to older patients difficult. Uncertainty in treatment benefits and costs can be mapped using decision analysis modeling. However, all modeling exercises utilize a set of assumptions that need to be evaluated and verified by future clinical trials. Nevertheless, this process may identify key questions for which future clinical trials can be designed.

In order to provide high quality medical care in the future several issues specific to older patients need to be resolved. These issues include: (1) the structure and selection criteria of clinical trials, (2) appropriate outcome measures for older patients, (3) improving communication regarding

benefits and side effects of treatment, (4) validated methodology to solicit treatment preferences from older patients, (5) individualizing treatment plans by taking into account both patient preference and the heterogeneity of comorbid disease burden and functional limitations, and finally (6) creating a prospective database to follow the many contributing factors that determine the type and care provided to older patients. These areas represent the future of outcomes and health services research in an older population.

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