

## RESEARCH ARTICLE

## Patients' preferences for selection of endpoints in cardiovascular clinical trials

Robert D. Chow, MD, MBA, FACP<sup>1\*</sup>, Kashmira P. Wankhedkar, MD<sup>2</sup> and Mihriye Mete, PhD<sup>3,4</sup>

<sup>1</sup>Department of Medicine, MedStar Good Samaritan Hospital, Baltimore, MD, USA; <sup>2</sup>Department of Medicine, Metropolitan Hospital Center, NYC Health and Hospitals Corps, New York, NY, USA;

<sup>3</sup>Department of Biostatistics and Epidemiology, MedStar Health Research Institute, Hyattsville, MD, USA; <sup>4</sup>Department of International Economics, School of Advanced International Studies (SAIS), Johns Hopkins University, Baltimore, MD, USA

**Background:** To reduce the duration and overall costs of cardiovascular trials, use of the combined endpoints in trial design has become commonplace. Though this methodology may serve the needs of investigators and trial sponsors, the preferences of patients or potential trial subjects in the trial design process has not been studied.

**Objective:** To determine the preferences of patients in the design of cardiovascular trials.

**Design:** Participants were surveyed in a pilot study regarding preferences among various single endpoints commonly used in cardiovascular trials, preference for single vs. composite endpoints, and the likelihood of compliance with a heart medication if patients similar to them participated in the trial design process.

**Participants:** One hundred adult English-speaking patients, 38% male, from a primary care ambulatory practice located in an urban setting.

**Key results:** Among single endpoints, participants rated heart attack as significantly more important than death from other causes (4.53 vs. 3.69,  $p=0.004$ ) on a scale of 1–6. Death from heart disease was rated as significantly more important than chest pain (4.73 vs. 2.47,  $p<0.001$ ), angioplasty/PCI/CABG (4.73 vs. 2.43,  $p<0.001$ ), and stroke (4.73 vs. 2.43,  $p<0.001$ ). Participants also expressed a slight preference for combined endpoints over single endpoint (43% vs. 57%), incorporation of the opinions of the study patient population into the design of trials (48% vs. 41% for researchers), and a greater likelihood of medication compliance if patient preferences were considered during trial design (67% indicated a significant to major effect).

**Conclusions:** Patients are able to make judgments and express preferences regarding trial design. They prefer that the opinions of the study population rather than the general population be incorporated into the design of the study. This novel approach to study design would not only incorporate patient preferences into medical decision making, but it also has the potential to improve compliance with cardiovascular medications.

Keywords: *Patient preferences; combined endpoints; clinical trial design; composite outcomes*

\*Correspondence to: Robert D. Chow, Department of Medicine, Russell Morgan Building Room 502, 5601 Loch Raven Boulevard, Baltimore, MD 21239, USA, Email: Robert.Dobbin.Chow@medstar.net

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Clinical trials play a pivotal role in clinical medicine, guiding the practice of medicine and the development of new guidelines. The design of clinical trials and the choice of trial endpoints have significant financial impact on the overall cost of the trial. To reduce the cost and duration of clinical trials, use of composite endpoints, in which at least two component outcomes are combined into a single composite outcome,

has become a popular choice for trial design in almost all fields of clinical medicine. The main advantages supporting the use of composite outcomes are as follows (1):

- The sample size can be reduced because of the higher number of events available in a composite outcome compared to a single outcome. As overall medical care has advanced over the past two decades, the general

improvement in the mortality of patients with cardiovascular disease has resulted in a higher number of patients who must now be enrolled in cardiovascular trials in order to demonstrate a mortality benefit and avoid a Type I error.

- The duration of the clinical trial can be reduced.
- Costs of the clinical trial can be substantially reduced, resulting in more trials conducted for a given amount of investment. Indeed, it is estimated that phase 3 clinical trials in 2006 cost \$26,000 per patient, and the rate is increasing at a rate of 4.6% per year (2).
- More rapid demonstration of the efficacy of a novel treatment can make a new drug more readily available to those in need.
- Investigators can avoid needing to choose a single endpoint to study. A single disease process can result in several important separate endpoints, such as heart attacks and strokes.

Because of these potential benefits, use of composite outcomes as a study design methodology has become commonplace in landmark, practice-changing clinical trials, as randomized controlled trials have become the new standard. In a review of 1,231 cardiovascular clinical trials conducted from 2000 to 2007, 37% used composite endpoints (3). Ideally, component outcomes should each be clinically meaningful, share the same biological effect or mechanism of action, contribute equally to the composite, and viewed with a similar degree of importance by patients (3). Unfortunately, those standards are not closely followed. In a review of 84 cardiovascular trials that used composite endpoints, 54% used endpoints with a wide range of importance to patients (4). The authors note that this practice may yield misleading impressions of the overall impact of the novel treatment, since higher event rates and larger treatment effects are associated with less important endpoints, such as hospitalization for chest pain, whereas more important endpoints, such as death due to myocardial infarction, were generally associated with lower event rates. Another author found inconsistent use of the composite endpoint approach across clinical trials, with flaws existing in both the methodology as well as the reporting of results (5), while another lamented, ‘The use of composite outcomes in trials is problematic. Components are often unreasonably combined, inconsistently defined, and inadequately reported. These problems will leave many readers confused, often with an exaggerated perception of how well interventions work’ (5).

A key but unrepresented party in the trial design decision-making process is the general public. Though patients, whose treatment is the ultimate goal of medical research, are the most important stakeholders in the design of clinical trials, they have not had a voice in the selection of trial design or the specific component endpoints.

We hypothesize that members of the general public can and desire to have a voice in the design of clinical trials. Yet, no studies have addressed patients’ preferences regarding the use of composite endpoints or the selection of the individual component endpoints. Such a study would not only provide valuable insight into patient preferences, but would also demonstrate that lay patients can understand study design methodology and express preferences.

## Methods

Adult patients from a primary care practice were asked to participate in a pilot study and express their opinions regarding use of endpoints in contemporary cardiovascular research trials. The study protocol was reviewed and approved by MedStar Health Institutional Review Board.

### Study design

Ambulatory patients were recruited from the patient population of an outpatient primary care office located in an urban setting. Consecutive patients were approached until the target of 100 participants was reached. A study coordinator administered a questionnaire to active participants and was available to answer questions if participants did not understand any portion of the survey. The initial part of the questionnaire included questions regarding demographic information (age, gender, ethnicity, and level of education). Patients were also asked if they had enrolled in any trial/s in the past and, if yes, then brief details regarding that trial were given.

In the latter part of the questionnaire, participants’ opinions regarding various endpoints commonly used in cardiovascular trials were requested. With a brief explanation about what a single and composite endpoint means, their preferences were solicited for single vs. composite endpoints, how a research study/trial should be designed, and how likely they would be to take a particular heart medication if they knew that patients similar to them participated in the decision-making process of selecting the trial endpoints that proved the medication to be efficacious.

The criteria for inclusion and exclusion are listed below.

### Inclusion criteria

Adults aged 18 years or older who are able to read and understand the questionnaire were included in the study.

### Exclusion criteria

- 1) Children and adolescents (age 18 years or younger)
- 2) Patients who cannot read English
- 3) Patients who are unable to understand the questionnaire.

The survey was administered until we had 100 participants. The responses were summarized using frequencies and percentages for categorical variables, and means and standard deviations for the continuous variables. Statistical comparisons between the rating scores for selected endpoints were made using paired *t*-tests for continuous variables and proportions tests for matched data for categorical variables. A copy of the survey is provided in the Supplementary file.

## Results

The demographic distribution of the sample population is listed in Table 1.

The participants were generally above 40 years of age, with Caucasians (52%) and African Americans (42%) comprising the major ethnic groups in the study. This is typical of the age group targeted by most cardiovascular trials. However, the ethnic distribution varies considerably among such trials, but most have far less African American participants. Approximately 75% of the sample population attended at least 2 years of college (Table 2).

Eleven percent of participants had participated in one or more clinical trials in the past. Though this number is low, those who have had experience with clinical trials in the past would presumably have enriched knowledge about clinical trials.

Table 3 lists the results of patients' perceptions of the importance of commonly used endpoints. Patients scored each endpoint on a scale from 1 to 6, with '1' representing 'least important' and '6' representing 'most important'.

**Table 1.** Demographic characteristics of the sample population

	%
<i>N</i> = 100	
Male	38
Age groups	
18–30	5
30–40	9
40–50	7
50–60	27
60–70	32
70+	20
Ethnicity	
Asian	4
Caucasian	52
African American	42
Hispanic	2
Others	0
Level of education	
High School/GED	26
2 years of college	20
4 years of college	18
Graduate school	36

**Table 2.** Participation in a clinical trial in the past

Participation in trial	Number of participants
No	89
Yes	11
Total	100

Most of the participants indicated that heart attack and death from heart disease were the most important endpoints to be included in a cardiovascular trial. Heart attack was rated as significantly more important than death from other causes (4.53 vs. 3.69,  $p = 0.004$ ), chest pain (4.73 vs. 2.47,  $p < 0.001$ ), angioplasty/PCI/CABG (4.73 vs. 2.43,  $p < 0.001$ ), and stroke (4.73 vs. 2.43,  $p < 0.001$ ). Death from heart disease was also rated higher in importance than death from other causes (4.53 vs. 3.69,  $p = 0.004$ ), chest pain (4.53 vs. 2.47,  $p < 0.001$ ), angioplasty/PCI/CABG (4.53 vs. 2.43,  $p < 0.001$ ), and stroke (4.53 vs. 2.43,  $p < 0.001$ ).

These findings suggest that patients prioritize the endpoints of heart attack and cardiovascular death in cardiovascular trials. In addition, the choice of these two endpoints may reflect the general concern in the population about the importance of these two conditions, and perhaps the uncertainty regarding the relevance of death from other causes as an endpoint in cardiovascular trials. Coronary revascularization and hospitalization for chest pain were relatively least important in comparison to the endpoints of cardiovascular death and heart attack. Notably, patients do not value all of these endpoints as being equivalent in importance, though clinicians and researchers treat all of the endpoints as equivalent in a composite endpoint analysis.

Table 4 lists the responses regarding a hypothetical cardiovascular trial comparing the efficacy of two cardiovascular medications.

In evaluating potential endpoints for this trial, nearly all participants selected heart attack as an endpoint that should be included in the trial design. A significantly higher proportion of respondents selected heart attack as an endpoint compared to death from heart disease

**Table 3.** Patient perception of the importance of common endpoints

Endpoint/importance	Mean score (SD) (95% CI)
Heart attack	4.53 (1.49) (4.2–4.8)
Death (heart disease)	4.73 (1.42) (4.5–5.0)
Death (other cause)	3.69 (1.78) (3.3–4.0)
Chest pain-hosp.	2.47 (1.24) (2.2–2.7)
Angioplasty/PCI/CABG	2.43 (1.18) (2.2–2.7)
Stroke	3.15 (1.53) (2.9–3.5)

**Table 4.** Choice of endpoint/s for a trial comparing two heart medications

Endpoint/response	No (%)	Yes (%)
Heart attack	9	91
Death (heart disease)	48	52
Chest pain-hosp.	48	52
Angioplasty/PCI/CABG	54	46
Stroke	35	65

( $p < 0.001$ ), chest pain ( $p < 0.001$ ), angioplasty/PCI/CABG ( $p < 0.001$ ), and stroke ( $p < 0.001$ ). Stroke was selected as significantly important more times compared to angioplasty/PCI/CABG ( $p < 0.007$ ) but not compared to chest pain and death from heart disease. The participants were more or less equivocal regarding the other proposed endpoints.

Participants were then surveyed regarding their choice of either a single or a composite endpoint. The results are provided in Table 5.

Participants expressed a preference for composite endpoints over single endpoints (57% vs. 43%). This result might be due to an inability to select a particular single endpoint over another (e.g., heart attack over death from heart disease).

Participants were then asked who should have input into the design of cardiovascular trials. The results are found in Table 6.

More participants recommended taking into account the opinions of the patient population (48%) over researchers/scientists (41%) or the general population (11%) in the decision-making process of trial design. At present, the trials are designed without input from the patient population or the general public, but solely by research investigators. If patients' preferences for selection of endpoints are considered, it is possible that study design would be significantly different from what is currently being selected by trial researchers.

Finally, participants were surveyed to see if their potential compliance to a cardiovascular medication would be affected if like-patients had contributed to the decisions regarding trial design of the trial. The results can be found in Table 7.

Participants acknowledged that if patients similar to them would have contributed to the trial design, and that

**Table 5.** Use of single vs. composite endpoints

Endpoint	Responses
Single	43
Composite	57
Total	100

**Table 6.** Potential contributors to the study design

Contributors	Responses
Researchers/scientists	41
Patient population	48
General public	11
Total	100

the trial demonstrated favorable results for a cardiovascular medication, then the participants would be more likely to comply with taking that medication. The active participation of like-patients would help dispel skepticism that the study was biased or influenced to yield positive results. The general public might have more confidence in the results, assuming that the patients who participate in the study design would have interests and perspectives similar to their own.

### Discussion

There are both benefits and problems associated with the use of composite endpoints. Though it is a validated statistical tool, it can potentially be utilized to the advantage and vested interest of the sponsor or the investigators. In addition, its use can lead to conclusions and clinical decisions that lack the precision of a single endpoint. The choice to utilize a composite endpoint trial design is usually made with the intention of reaching a positive result in the shortest amount of time and consuming the least amount of resources. As healthcare resources are being curtailed, funding sources for clinical trials will become scarcer, and the use of composite endpoints will become more widespread.

Though patients may have harbored personal opinions regarding study methodology based on their values and experiences, there has not been an opportunity to for patients to articulate their views regarding a preferred study design. Patients and investigators might value potential clinical outcomes or endpoints differently. If patients are given an opportunity to voice their opinions regarding study design and choice of component outcomes, such an

**Table 7.** Effect on participants' potential compliance to a cardiovascular medication if patients similar to participants had contributed to the decision-making process for trial design

Effect on compliance	Responses
No effect	8
Small effect	25
Significant effect	39
Large/major effect	28
Total	100

approach may provide richer and more meaningful results to future patients. Future studies may demonstrate that patients can potentially make insightful recommendations regarding the choice of endpoints as well as value judgments regarding each proposed endpoint that is in the best interest of patients. If patients select composite outcomes as their preferred methodology for a given trial, then they should also have a voice in designating the specific component outcomes that should be included in the composite. Finally, if the target population contributes to the study design and selection of endpoints, this may potentially impact the compliance of this population with the study medications, once the study results are disseminated. That is, the nature, design, and results of any study will be perceived with greater validity if participants' perceptions are taken into account.

As medical treatments are becoming more sophisticated and evidence-based, the opinions and preferences of patients may be more challenging to integrate into clinical research methodology. However, as noted by Quill et al., who coined the term preference-based care, good patient care is a delicate balance between evidence-based care, patients' preferences, and societal values (6). We believe that the same concept can be extended to clinical research, which has yet to directly embrace the preferences of patients into its regular study design decision-making process.

In our study, patients seemed to prefer the use of a composite endpoint over single endpoints. However, those with a higher level of education expressed a preference for the single endpoint methodology. The reason is open to speculation and provides cause for further investigation. Further, our survey showed that it more important to survey the patient population rather than the general population regarding study methodology. The distinction between these two groups seems to be important; the former has insight into the disease experience and a vested interest in the outcome.

Finally, one criticism regarding composite endpoints is the relative inequality among the endpoints. For example, patients seem to value the endpoint of myocardial infarction with greater importance than hospitalization for chest pain. Investigators have also lamented the choice of unequal endpoints in composite endpoint trials (7). However, it may be possible to adjudicate each element of the composite endpoint with an empirically-derived

adjustment factor based on pre-stated patient preferences and values. Thus, meeting a less-valued component of the composite endpoint, such as hospitalization for chest pain, may not necessarily mandate that the composite endpoint has been reached. Such an approach would require general acceptance from the entire scientific community in terms of how such an approach might be implemented.

This is pilot study and is limited by the small sample size. In addition, our sample has a higher level of education compared to the general U.S. population; 8% of the U.S. population has a Master's degree education (9), compared to 34% of our sample. Further studies with larger sample sizes would help confirm the need to solicit patient input into the process of study design development.

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