Novel methods in preference-based health outcome measurement

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English Summary

Measuring subjective health outcomes (or patient-reported outcomes, well-being, health status, health-related quality of life) has gained substantial recognition, beyond traditional clinical indicators (e.g., survival, blood pressure). Distinct categories of health outcome measures have been developed to measure subjective health outcomes. They are constructed through diverse measurement frameworks, such as preference-based measures. Preference-based measures specially assign weights (importance) to health items and levels of items (attribute levels). These weights can be further computed to produce a single index that expresses the (social) value of a health state. Such values are meaningful in monitoring population's health, assessing healthcare interventions, comparing health status across different populations. Especially, when normalized into utilities which range from 0.0 (dead) to 1.0 (full health), they are applicable to conduct cost-effectiveness analysis in health economic evaluations.

Challenges remain in existing preference-based PROMs (e.g., no patient involvement in their development, limitations remain in preference-based methods). Trying to make some improvements to the current preference-based PROMs, we introduced a novel measurement framework (multi-attribute preference response, MAPR) for developing health outcome measures. The MAPR framework integrated a patient-centered, preference-based PROM (CS-Base), a novel and simpler preference-based method (Drop-Down), and user-friendly electronic mobile applications. In this thesis, we introduced two new preference-based methods developed within the MAPR framework and compared them head-to-head (**Chapter 2**); We parallelly compared the CS-Base with the widely-used EQ-5D-5L, to explore the effects of different measurement frameworks and descriptive systems (**Chapter 3**); We also reported the results of a preliminary application of CS-Base in comparing health status across various health conditions (**Chapter 4**); Finally, a first CS-Base utility set was generated for its application in health economic evaluations (**Chapter 5**).

Chapter 2

In the second chapter, two new preference-based methods which are both developed within MAPR framework are compared: the previously developed Better-Worse (BW) and the expanded Drop-Down (DD) methods. We compared them regarding the statistics of their estimated coefficients, the distribution of the computed health-state values, and their user experience. The BW method entails paired comparison of patients' own health states with hypothetic

health states. While in the DD method, only patients' own health states are presented, they are asked to select health items that disturb them most for several times. The study results showed that both BW and DD coefficients demonstrated good face validity, with *comparable* coefficients of each level observed *across all the 12 items*. D*ifferences between the levels* of all items were clearly noticeable. However, the DD method apparently outperformed the BW method in producing more precise coefficients. All the DD coefficients showed high statistical significance and small confidence intervals, while that was not the case for the BW coefficients. Consequently, the DD method produced results with both statistical robustness and good face validity.

Chapter 3

The third chapter compared two generic preference-based health outcome measures: the CS-Base and the EQ-5D-5L. The descriptive systems and measurement frameworks differ between two measures. The EQ-5D-5L has the advantage of brevity with only five items. However, questions arise as to whether the five items measure patients' health status sufficiently as they are not selected by patients but by researchers. Additionally, in EQ-5D-5L valuation studies, health preferences are collected from the general population instead of patients. Furthermore, the preference-based method (TTO) as applied to the EQ-5D instruments is associated with limitations aforementioned. Therefore, we intended to compare the two measures, to explore the effects of different measurement frameworks and descriptive systems. Another measure the 5D-4L L (an ad hoc, MAPR-based measure that includes five items similar to the EQ-5D-5L, but with four levels) was added to reduce the discrepancies between the CS-Base and EQ-5D-5L, which might lead to incomparability of the results of the two health outcome measures.

According to each paired comparison of the three measures, for the CS-Base versus 5D-4L (using the same measurement framework), both produced statistically robust coefficients and showed good face validity. However, probably due to more items included in the descriptive system, the CS-Base demonstrated better differentiation between health states. For the 5D-4L versus EQ-5D-5L (based on different measurement frameworks), the coefficients of the 5D-4L showed better face validity than those of the EQ-5D-5L. The EQ-5D-5L outperformed 5D-4L in differentiating health states with a similar descriptive system (similar items but different levels), but with different administration modes (one-screen and separate-screens display for items). As for the comparison of CS-Base versus EQ-5D-5L, notwithstanding differences in

content, applied measurement frameworks, and estimated coefficients, the computed health-state values were rather similar between the CS-Base and EQ-5D-5L.

Chapter 4

The fourth chapter reported the results of a preliminary application of the CS-Base to compare the health status of patients with one or more health conditions. Most existing research studying health status impacted by morbidity has focused on a specific health condition, and most health outcome measures used are neither patient-centered nor preference-based. This study aimed to bring some new insights into the research of health status of morbidity. This was done by comparing health status across various health conditions directly, using the single metric value measured by the patient-centered and preference-based ePROM.

We compared health-state values measured by the CS-Base between sociodemographic subgroups, between separate conditions, between groups with or without comorbidity, and between different combinations of multimorbidity. Our results showed that multimorbidity was present in more than half of the patients. The most prevalent health conditions were pain, fatigue/sleep problems, mental health problems, respiratory diseases, and diabetes. The highest (best) and lowest health-state values were observed in patients with diabetes and mental health problems. Among combinations of multimorbidity, the lowest values were observed when mental health problems were involved, the second lowest values were observed when fatigue/sleep problems and respiratory diseases coexisted.

Chapter 5

The fifth chapter described how a first utility set for the CS-Base has been generated using a two-step approach. In previous studies, we have generated a value set for the CS-Base. However, these values are not utilities thus not applicable in health economic evaluations, as they are not anchored around the position of "dead". To create a utility scale (0.0–dead to 1.0–full health), we conducted this study to rescale these values. We first derived coefficients for attribute levels and computed CS-Base values using the data collected by tasks within MAPR framework (MAPR tasks) based on a patient sample. In the second step, we normalized the values derived . The location of "dead" ("0.0") was estimated using data collected using the discrete choice experiment with Dead (DCE+Dead) based on a general population sample.

Statistically robust coefficients were estimated from the regression analysis, using MAPR data collected from patients. The values for all possible CS-Base states ranged from -158.763

to 0.0. The location of "dead" was represented by an estimated division value (-148.385) which distinguished states that were better than dead (BTD) from those worse than dead (WTD), using the DCE+Dead data collected from respondents of the general population. The generated utilities (normalized values) ranged from -0.071 to 1.0 . A negligible number (53, 0.0003%) of states was considered WTD. Consequently, this study generated a first utility set for the CS-Base. This two-step approach has several advantages in generating utilities for health outcome measures as it combines both societal and patient perspectives, it also overcomes some drawbacks of conventional preference-based methods and produces more robust results.

In summary, this thesis centered around the performance of the novel MAPR measurement framework developed for application in preference-based health outcome measurement. The generic ePROM CS-Base and the new preference-based DD method founded on the MAPR framework are studied. The statistical robustness and feasibility of the DD method have been confirmed by our study. The performance of the CS-Base regarding its differentiation between health states has been validated, by comparing it with the widely used EQ-5D-5L. The first clinical application of the CS-Base in measuring and comparing health status across various health conditions has also been presented in this thesis.

Nederlandse samenvatting

Het meten van subjectieve gezondheidsuitkomsten (ook wel gezondheidstoestand, welzijn of gezondheidsgerelateerde kwaliteit-van-leven genoemd) heeft meer aandacht en erkenning gekregen. Deze uitkomsten kunnen gezien worden als een aanvulling op traditionele klinische maten zoals overleving en bloeddruk. Tevens zijn er verschillende theoretische modellen om zulke gezondheidsuitkomsten te meten. Wanneer zulke uitkomsten worden verkregen door responses van patiënten, worden dergelijke uitkomsten en hun metingen vaak aangeduid als 'patient-reported outcome measures': PROMs. Er zijn verschillende typen instrumenten ontwikkeld om subjectieve gezondheidsuitkomsten te meten. Een voorbeeld hiervan zijn meetinstrumenten waarbij respondenten voorkeuren of preferenties moeten aangeven. Op basis hiervan kunnen gewichten (mate van belangrijkheid) worden toegekend aan de antwoordcategorieën van items die ieder gerelateerd zijn aan een specifiek gezondheidsdomein. Deze gewichten kunnen worden gebruikt om een index te produceren die de (sociale) waarde van een algehele gezondheidstoestand (een set van gezondheidsdomeinen) uitdrukt. Zo'n index of waarde is zinvol bij het monitoren van de gezondheid van een groep mensen, het evalueren van gezondheidszorginterventies en het vergelijken van de gezondheidstoestand tussen verschillende groepen. Wanneer zulke waarden zijn genormaliseerd (utiliteiten) en variëren van 0.0 (dood) tot 1.0 (volledige gezondheid), zijn ze breed inzetbaar bij economische evaluaties in de gezondheidszorg.

Er zijn een aantal uitdagingen bij het gebruik van de huidige meetinstrumenten gebaseerd op preferenties. In een poging om enkele verbeteringen aan te brengen in de huidige methodiek van deze meetinstrumenten hebben we een nieuw meetmodel geïntroduceerd, het 'multi-attribuut preference response' (MAPR) model. Het MAPR model omvat een nieuwe en eenvoudige preferentie methode in combinatie met gebruiksvriendelijke mobiele software. In dit proefschrift hebben we twee nieuwe preferentie methoden geïntroduceerd die zijn ontwikkeld binnen het MAPR model en deze met elkaar vergeleken (**Hoofdstuk 2**). De EQ-5D-5L, een veelgebruikte preferentie meetinstrument, is parallel vergeleken met een door ons ontwikkelt preferentie meetinstrument en tevens PROM: de CS-Base (**Hoofdstuk 3**). We rapporteerden ook de resultaten van een eerste toepassing van de CS-Base bij het vergelijken van de metingen van de gezondheidstoestand bij patiënten met verschillende gezondheidsaandoeningen (**Hoofdstuk 4**). Ten slotte werd een utiliteitswaarde voor de CS-Base gegenereerd voor toepassing in economische evaluaties in de gezondheidszorg (**Hoofdstuk 5**).

Hoofdstuk 2

In het tweede hoofdstuk werden twee nieuwe preferentie methoden, die beide zijn ontwikkeld binnen het MAPR model, met elkaar vergeleken: de eerder ontwikkelde Better-Worse (BW) en de aangepaste Drop-Down (DD) methode. We vergeleken ze op basis van de statistische eigenschappen van de geschatte coëfficiënten, de verdeling van de berekende waarden voor verschillende gezondheidstoestanden en de ervaring van gebruikers. Het instrument dat hiervoor werd ingezet was de CS-Base. In de BW-methode krijgen patiënten gezondheidstoestanden ter beoordeling aangeboden die vrijwel overeenkomen met hun eigen gezondheidstoestanden. Daarentegen worden in de DD-methode alleen de gezondheidstoestanden van patiënten gepresenteerd en wordt gevraagd om de gezondheidsitems te selecteren die voor hen het meest hinderlijk zijn. De resultaten van de studie laten zien dat zowel BW- als DD-coëfficiënten op het oog valide lijken te zijn. Voor alle 12 items was de ordening van de coëfficiënten vergelijkbaar. De DD-methode bleek echter duidelijk beter te presteren. Alle DD-coëfficiënten vertoonden hoge statistische significantie en kleine betrouwbaarheidsintervallen, terwijl dat niet het geval was voor de BW-coëfficiënten. Als gevolg daarvan produceerde de DD-methode resultaten met zowel statistische robuustheid als goede 'face' validiteit (face validity).

Hoofdstuk 3

In het derde hoofdstuk wordt de vergelijking van twee instrumenten beschreven: de CS-Base en de EQ-5D-5L. De beschrijvende systemen en meetmodellen van deze twee generieke en op preferentie gebaseerde instrumenten zijn verschillend. De EQ-5D-5L heeft als voordeel dat het met slechts vijf items bondig is. Men kan zich echter afvragen of met slechts vijf items de gezondheidstoestand van patiënten afdoende in kaart gebracht kan worden. Tevens waren deze vijf items niet geselecteerd door patiënten maar door onderzoekers. Daarnaast worden voorkeuren voor gezondheidstoestanden gemeten in de algemene bevolking, in plaats van bij patiënten. Bovendien zijn de preferentie-methoden die worden toegepast voor de EQ-5D-5L geassocieerd met verschillende verstorende factoren. Daarom zijn de twee instrumenten vergeleken om de effecten van verschillende beschrijvende systemen en meetkaders te verkennen. Een ander instrument, de 5D-4L (een ad-hoc, op MAPR gebaseerd instrument met vijf items die vergelijkbaar zijn met de EQ-5D-5L, maar net als de CS-Base met vier antwoord categorieën), werd toegevoegd om de verschillen tussen de CS-Base en EQ-5D-5L te verkleinen, en zo de vergelijkbaarheid te vergroten.

In de vergelijking tussen de 5D-4L en de EQ-5D-5L (gebaseerd op verschillende meetmodellen), vertoonden de coëfficiënten van de 5D-4L een betere 'face' validiteit dan die van de EQ-5D-5L. De EQ-5D-5L presteerde beter dan de 5D-4L in het differentiëren van gezondheidstoestanden met een vergelijkbaar beschrijvend systeem. Wat betreft de vergelijking tussen de CS-Base en de EQ-5D-5L, ondanks de verschillen qua inhoud, toegepaste meetmodel en geschatte coëfficiënten, waren de berekende waarden voor de verschillende gezondheidstoestanden redelijk vergelijkbaar. Echter, de CS-Base bleek in staat om beter te differentiëren tussen verschillende gezondheidstoestanden, waarschijnlijk omdat dit instrument meer items bevat.

Hoofdstuk 4

In het vierde hoofdstuk werden de resultaten gepresenteerd van een vroege toepassing van de CS-Base om de waarde van de gezondheidstoestand van patiënten met één of meer gezondheidsaandoeningen te vergelijken. De meeste bestaande onderzoeken hiernaar hebben zich gericht op een specifieke aandoening en de gebruikte instrumenten zijn ontwikkeld zonder volledige patiënt participatie, noch gebaseerd op metingen waarbij preferenties en wegingen een rol spelen. Dit onderzoek had tot doel nieuw inzicht te brengen door de waarde van gezondheidstoestanden te vergelijken tussen patiënten met verschillende aandoeningen (ziekten of klachten).

De gemeten waarden met behulp van de CS-Base werden vergeleken voor sociodemografische subgroepen, groepen patiënten met afzonderlijke aandoeningen, groepen met of zonder comorbiditeit, en combinaties van multimorbiditeit. Onze resultaten toonden aan dat multimorbiditeit aanwezig was bij meer dan de helft van de patiënten. De meest voorkomende aandoeningen waren pijn, vermoeidheid/slaapproblemen, psychische klachten, luchtwegaandoeningen en diabetes. De hoogste (beste) en laagste waarden werden respectievelijk waargenomen bij patiënten met diabetes en psychische gezondheidsproblemen. Onder combinaties van multimorbiditeit werden de laagste waarden waargenomen wanneer psychische gezondheidsproblemen aanwezig waren. De op één na laagste waarde werd waargenomen wanneer vermoeidheid/slaapproblemen en luchtwegaandoeningen beiden aanwezig waren.

Hoofdstuk 5

Het vijfde hoofdstuk beschrijft hoe voor de CS-Base utiliteiten worden gegenereerd met behulp van een tweestap benadering. In eerdere onderzoeken hebben we waarden gegenereerd voor CS-Base gezondheidstoestanden. Deze waarden zijn echter geen utiliteiten en daarom niet toepasbaar in gezondheid-economische evaluaties, omdat ze niet zijn geankerd op "dood". Om een

utiliteit (0.0 = dood, tot 1.0 = volledige gezondheid) te creëren werden in dit onderzoek de waarden opnieuw geschaald. Eerst zijn de coëfficiënten voor de antwoordcategorieën van de 12 CS-Base items geschat. Op basis hiervan zijn de CS-Base waarden voor de gezondheidstoestanden berekend. De gegevens werden verzameld op basis van de Drop-Down methode in een groep patiënten (Hoofdstuk 2). In de tweede stap zijn de afgeleide waarden genormaliseerd. De positie van "dood" ("0.0") werd geschat met behulp van gegevens verzameld met behulp van een discreet keuze-experiment waarin 'dood' een rol had (DCE+Death). Hiervoor gebruikten wij een steekproef uit de algemene bevolking.

De coëfficiënten die geschat werden in de regressieanalyse bleken robuust. De waarden voor alle mogelijke CS-Base toestanden varieerden van -158.763 tot 0.0. De positie van "dood" werd gerepresenteerd door een geschatte afkapwaarde (-148.385) die gezondheidstoestanden die beter waren dan dood onderscheidde van staten die slechter waren dan dood (WTD). De gegenereerde utiliteiten (genormaliseerde waarden) varieerden van -0.071 tot 1.0. Een verwaarloosbaar aantal (53, 0.0003%) gezondheidstoestanden werden beschouwd als slechter dan dood. Als gevolg hiervan heeft dit onderzoek een eerste set van utiliteiten gegenereerd voor de CS-Base. Deze tweestap benadering heeft verschillende voordelen voor het genereren van utiliteitswaarden voor gezondheidstoestanden. Ten eerste, omdat de schattingen van de coëfficiënten gebaseerd zijn op een eenvoudige doch krachtige meetmethode uitgevoerd door ervaringsdeskundigen (patiënten). Voor de herschaling worden maatschappelijke waarderingen gebruikt, die echter niet de reeds geschatte coëfficiënten kunnen verstoren. Ten tweede, omdat bepaalde nadelen die samenhangen met de conventionele preferentie methoden worden vermeden. Ten derde, omdat deze benadering resultaten produceert die robuust zijn.

Samenvattend beschrijft dit proefschrift eigenschappen en resultaten van het nieuwe MAPR-meetmodel dat is ontwikkeld voor het meten van gezondheid bij en door patiënten gebaseerd op preferenties. De generieke (elektronische) PROM CS-Base en de nieuwe DD preferentiemethode, gebaseerd op het MAPR meetmodel, zijn bestudeerd. De statistische robuustheid en haalbaarheid van de DD-methode zijn bevestigd door ons onderzoek. De prestaties van de CS-Base met betrekking tot de differentiatie tussen gezondheidstoestanden zijn gevalideerd in een vergelijking met de veelgebruikte EQ-5D-5L. Ten slotte is de eerste empirische toepassing van CS-Base bij het meten en vergelijken van de gezondheidstoestand bij verschillende gezondheidsaandoeningen uitgevoerd en gepresenteerd in dit proefschrift.

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