Scoping review on preferences and trials

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Scoping review on preferences and trials

The application of preference elicitation methods in clinical trial design to quantify trade-offs: A scoping review

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Guarantor of the article: Megan Thomas

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Scoping review on preferences and trials

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ABSTRACT

Background and Objective: Patients can express preferences for different treatment options in a healthcare context, which can be measured with quantitative preference elicitation methods. Our objective was to conduct a scoping review to determine how preference elicitation methods have been used to design clinical trials.

Methods: We conducted a scoping review to identify primary research studies involving any health condition, that used quantitative preference elicitation methods, including direct utility-based approaches, and stated preference studies, to value health trade-offs in the context of clinical trial design. Studies were identified by screening existing systematic and scoping reviews, and a primary literature search in MEDLINE from 2010-present. We extracted study characteristics and the application of preference elicitation methods to clinical trial design according to the SPIRIT checklist from primary studies and summarized the findings descriptively.

Results: We identified 18 eligible studies. The included studies applied patient preferences to 5 areas of clinical trial design: intervention selection (n=1), designing N-of-1 trials (n=1), outcome selection and weighting composite and ordinal outcomes (n=12), sample size calculations (n=2), and recruitment (n=2). Using preference elicitation methods led to different decisions being made, such as using preference-weighted composite outcomes instead of equally weighted composite outcomes.
Conclusion: Preference elicitation methods are infrequently used to design clinical trials but may lead to changes throughout the trial which could impact the evidence generated. Future work should be done to consider measurement challenges and explore stakeholder perceptions.

Key words: Patient preference, Clinical trial, Review

Key points:

- To our knowledge, no review has been conducted to consider the application of quantitative preference elicitation methods to trial design across health conditions.
- Patient preference information can be used to design trials that address patient priorities, values and needs including the selection of outcomes and interventions, determining sample size, and estimating recruitment.
- Using preferences to design trials could change the way evidence is generated by including patient priorities to help ensure the information gathered is more relevant to patients.

1. Introduction

Patients must often make trade-offs when choosing between different treatments. A preference is broadly defined as an “individual’s expression of desirability or value of one course of action, outcome, or selection in contrast to others” (1). Patients can express preferences for different treatment options in healthcare which may reflect trade-offs according to personal preferences, values and needs. Quantitative preference elicitation methods can elicit patient preferences to assign a preference weight to the relevant trade-offs (2,3).
There are different approaches used within quantitative preference elicitation methods. Direct utility-based approaches ask patients to choose between staying in a given health state or a gamble that has a certain probability of an immediate return to full health but also a chance of immediate death (standard gamble) or shortened life expectancy (time trade-off, TTO) (4). Actual decisions (revealed preferences) can be used, however when this is not possible, as is often the case in healthcare, stated preference methods can provide important information. Stated preference methods, such as discrete choice experiments (DCEs), require patients to choose, rate, or rank a set of hypothetical treatment alternatives (5). Preference elicitation methods provide value weights for the trade-offs that should be considered when making treatment decisions.

There is guidance for best practices when conducting preference studies (5,6) and on how these methods could be applied in health technology assessment (7,8). However, to our knowledge, there is no comprehensive assessment or guidance on how these methods can and should be applied to clinical trial design. There are many aspects of clinical trial design where value judgements are required or may be helpful, from selecting outcomes and determining what an important difference is, to estimating patient recruitment or structuring complex interventions to maximize their potential benefit. These value judgements are traditionally made by the researchers conducting the trial, however, there is an opportunity to include patient voices when designing clinical trials, which could improve how evidence is generated. The aim of this scoping review was to identify and categorize approaches in which preference elicitation
Scoping review on preferences and trials

methods have been applied to clinical trial design in order to value trade-offs relevant to clinical
decision-making.

2. Methods

2.1 Protocol

A protocol was developed using the Joanna Briggs Institute (JBI) scoping review methodological
framework (9). The final protocol is available upon request from the corresponding author. A
scoping review was chosen over a systematic review, as our aim was to map out applications on
the use of preference elicitation methods to design clinical trial. Scoping reviews are particularly
useful when considering novel concepts, or areas where not much is known on the subject (10).
Systematic reviews, in contrast, are important when the goal is to synthesize all information on a
particular clinical question and are typically more appropriate for more well-established topic
areas.

2.2 Inclusion criteria

We included primary research studies involving any health condition, that used quantitative
preference elicitation methods to value health trade-offs in the context of clinical trial design. We
used a broad definition of quantitative preference elicitation methods, including any study that
provided quantitative information on the relative or absolute importance of health or treatment
related attributes. This included both direct utility-based approaches and stated preference
studies, as well as other approaches such as visual analogue scales (VAS), which are not
typically preference elicitation methods or rooted in economic theory (11,12). The application of
preferences had to be related to the design of clinical trials; studies were excluded if the authors
did not demonstrate the applicability to trial design within the study. We also excluded patient preference trials, which compare outcomes between patients whose treatment was allocated based on their preferences to patients whose treatment was randomly allocated, unless they specifically measured patient preferences and used these to inform the trial design (13). There was no restriction regarding the time or country of publication. Studies were excluded if they were not in English or if they were conference abstracts or protocols.

2.3 Information sources and search

To identify relevant articles, we used a staged search strategy. In the first stage, given the breadth of the topic, and the increasing number of systematic reviews of patient preference studies, we conducted a search of systematic and scoping reviews to identify a broad sample of primary studies. Reviews were identified through a search of the electronic databases MEDLINE (Ovid, 1946 to present) and EMBASE (Ovid, 1984 to present) from inception to November 2019, by combining established MeSH and Boolean search filters for “review/systematic review/guideline” with a filter for “preference elicitation methods” that we have previously used (4). After a screen of 33 reviews, which included several comprehensive reviews spanning multiple health conditions (4,14,15), we identified only 2 eligible primary studies. Therefore, in the second stage, we expanded our search to identify primary studies in MEDLINE from 2010-December 2020 by combining the same search filter for preference elicitation methods with a search filter for clinical trial design (See supplementary materials). The search strategy was then revised in an iterative process. We were aware of certain references which should be identified through a successful search strategy which guided our search modifications (16–18). Finally, we
also hand-searched reference lists of included studies and asked our research team to identify relevant studies.

2.4 Study selection
All retrieved publications were independently screened by MT and DC for eligibility, first by title and abstract, then by full text. Any records judged eligible by either reviewer proceeded to full text review. Disagreements during the full-text screening were resolved by consensus and discussed with a third reviewer (GH) where there was uncertainty.

2.5 Data extraction and synthesis of results
Data extraction of the primary studies included authors, title, journal, year, country, health condition, preference elicitation method used, stated purpose for using preference elicitation method, and application to clinical trial design. This allowed us to map the studies to where they have been applied along the stages of clinical trial design. To identify the stages of clinical trial design, we reviewed different reporting checklists for clinical trials including Consolidated Standards of Reporting Trials (CONSORT) (19) and Standard Protocol Items and Recommendations for Interventional Trials (SPIRIT) (20). We chose to categorize each included study to steps outlined by the SPIRIT checklist, as SPIRIT is used to inform the development of trial protocols, whereas CONSORT is used to inform the way trials are reported. The SPIRIT checklist includes 33 items across 5 sections (Administrative Information, Introduction, Methods, Ethics and Dissemination, and Appendices). We used the Introduction and Methods section items to categorize included studies according to their application to trial design. We developed a table, mapping included studies to SPIRIT checklist items. We also included a
Scoping review on preferences and trials

narrative summary of our tabulated results to describe the information gained from using
preference elicitation methods and how the information was applied within the context of the
study. Where multiple studies used a similar approach, we selected case examples for the
narrative summary, aiming for diversity in the clinical settings represented.

Following best practices, the review was conducted with consultation of librarians and content
experts throughout (9). As our aim was to describe where and how preference elicitation
methods have been applied in clinical trial design, we did not appraise methodological quality or
risk of bias of the included studies, consistent with best practices on scoping reviews (9).

3. Results

3.1 Study selection

From our search of primary studies, we identified 13 articles, after screening 5419 unique
records (Figure 1). Five additional studies were identified: two from our initial search of reviews;
one from hand searching reference lists; and two from members of our research team, one of
which had been previously presented as an abstract but not a full-text article prior to our database
search. The inclusions were pooled for a total of 18 included primary studies (16–18,21–35).

3.2 Study Characteristics

The characteristics of included studies are summarized in Table 1. The studies were largely
conducted between 2016-2020. All studies were conducted in academic centers in North
America, Europe, or the UK. The health conditions were diverse, but the most common field was
Cardiology (n=7). The studies used a wide range of preference elicitation methods which are listed in Table 1 and defined in Table 2.

3.3 Applications to Trial Design

The included studies demonstrated application of preferences to five areas of trial design in the SPIRIT checklist section within Introduction/Methods: Intervention selection, Trial design, Outcome selection, Sample size, and Recruitment (20).

3.3.1 Intervention selection

In one study, researchers used a DCE to inform the selection of interventions. Morgan et al. conducted a DCE, embedded within a larger study, on smoking cessation in pregnancy and determined that the results could be used to inform future trials of incentives (26). The DCE results suggested that no incentive or an incentive of £20 per month had negative effects on the likelihood of quitting whereas an incentive of £40 or £80 per month had a positive effect.

3.3.2 Trial design

In one study, preferences were elicited for various aspects of trial design included in the SPIRIT checklist, with an application to N-of-1 trials (22). Cheung et al. used conjoint analysis (CA) to elicit individual preferences for attributes of trials in chronic diseases, such as the type of treatment selected (pharmacological, lifestyle change, or alternative medicine), participant burden (time commitment, frequency of data collection, and study duration), and logistics (blinding or no blinding). The results displayed preference heterogeneity across attributes, which suggested a need to personalize design features of trials to account for individual differences,
based on the attributes participants deem desirable. While the researchers demonstrated the value of using patient preferences to inform the design of N-of-1 trials, their findings could also be applicable to traditional clinical trials.

3.3.3 Outcome selection

The most common application to clinical trial design was outcome selection (n=12). Within outcome selection, the 3 applications were: prioritizing outcomes, weighting composite outcomes, and weighting ordinal outcomes.

Prioritizing outcomes

In three studies, the researchers used preference elicitation methods to inform outcome selection for their study (17,23,24). Stamuli et al. used a DCE to elicit preferences for patients with rheumatoid arthritis, where the most highly valued outcome from the DCE would inform the choice of the primary outcome in a trial of rehabilitation/health and fitness strategies for patients (24). Patients weighted foot and ankle pain as the most important outcome, with mobility being nearly as important, which the researchers identified as key primary and/or secondary outcomes that should be measured in subsequent clinical trials. Overall, they concluded that when dealing with uncertainty in treatment options, patient preferences should be elicited to prioritize outcomes and inform trial design.

Weighting composite outcomes

Composite outcomes were developed using preference weights in eight studies, making it the most frequent application to trial design in this review (16,18,25–30). Tong et al. used a DCE to
inform the weights of components of a composite outcome for cardiovascular trials (16). The researchers found that as compared with assigning equal weights to each component, using a preference-weighted outcome affected how the trial results were interpreted and could impact decision-making in cardiovascular treatments. The patients did not assign equal weights to each part of the composite outcome being measured. Instead, patients ranked risk of death as most important, followed by stroke, potential increased longevity and recovery time, myocardial infarction, and risk of repeat revascularization. Metcalfe et al. elicited preferences through BWS Case 2 to determine the relative importance of each intervention and outcome in the management of hypertension in pregnancy using patient level data from the Control of Hypertension in Pregnancy Study trial (18). Latent class analysis identified three preference profiles which were used to calculate composite endpoints. Using a preference-weighted composite outcome changed the recommendations for patients as the recommended intervention varied by preference profile, speaking to the diversity of preferences in the management of pregnancy hypertension and the impact of this heterogeneity on the interpretation of clinical trial results. Recognizing that the current approach to composite outcomes fails to account for preference heterogeneity, Butler et al. used preference elicitation to estimate individualized composite outcomes, which they applied to a clinical trial on anti-psychotic medications for schizophrenia (26). They proposed a method to develop preference-sensitive composite outcomes for each patient, which could have important applications to trial design and downstream in the shared decision-making process for patients.

**Weighting ordinal outcomes**
One study used preference elicitation methods to weigh the severity of the modified Rankin scale (mRS), a scale used to measure the level of disability in daily activities for patients who suffered a stroke (31). The mRS is a common primary end point in acute stroke trials and is usually analyzed in either a dichotomous or ordinal fashion. By weighting the severity of the mRS according to patient preferences, the researchers were able to derive a utility-weighted mRS, which allowed for comparing the relative importance of each severity category in the mRS. They found that using a utility-weighted mRS compared similarly to the standard (unweighted) mRS in statistical relevance while also improving interpretability of acute stroke trial results for patients.

### 3.3.4 Informing worthwhile effect sizes and sample size calculations

When determining the sample size of a trial, researchers must judge the threshold for an important difference in the primary outcome. A smallest worthwhile effect (SWE) is defined as the smallest treatment effect that justifies the costs, risks and inconveniences associated with that intervention, based on their relative importance (36). Franco et al. used two preference elicitation approaches, including a DCE and benefit-harm trade-off, to estimate the SWE of exercise programs designed to prevent falls among older people (32). They found that a large proportion (82% in the discrete choice experiment and 50% in the benefit–harm trade-off study) of participants would choose not to participate in an exercise program designed to prevent falls, even if it reduced their risk of falling to 0%.

In another example related to sample size calculations, Chaudhuri et al. demonstrated that patient preferences can be used to assign weights to type I and II errors in trials for new treatments (33).
Using a case study assessing weight-loss medical devices, the researchers showed that when an intervention is considered low-risk, it may be appropriate to set a higher significance level (or increase the risk of type I error), which subsequently would require fewer participants to show a difference. Conversely, they show that with high-risk interventions, a lower significance level may be appropriate, requiring more participants to show a significant difference. The researchers conclude that the optimal number of trial participants varies according to patient preferences around risk, and this should be incorporated in trials to maximize value for patients, i.e., providing patients with a safe and effective treatment, or concluding that a treatment is not reasonably safe or effective, as soon as possible.

3.3.5 Recruitment

Preference elicitation methods were used to estimate potential participant enrollment in future randomized controlled trials (RCT) in two studies (34,35). Kerman et al. used a simple stated preference assessment to ask patients about their willingness to participate in a hypothetical trial for knee pain, and their treatment preferences (34). They found that patients with no treatment preferences were more likely to participate compared to those who had a definitive treatment preference. Smith et al. used CA to examine preferences for RCT characteristics among individuals with chronic pain conditions who would consider participating in pharmacologic pain treatment trials (35). The three characteristics with the highest relative importance were: laboratory procedures, ability to remain on current pain medications, and payment. The researchers recommended a balance between researcher and patient priorities in trials, as doing so may improve participant enrollment in pain management trials.
4. Discussion

This scoping review identified 18 studies that applied preference elicitation methods to clinical trial design across a range of health conditions. Most studies used preference elicitation methods to inform outcome selection, but there were other applications relevant to trial design as well, including sample size and recruitment. Many of the applications led to different decisions than may have otherwise been made by trialists, highlighting the potential impact of a systematic consideration of patient preferences on clinical trial design. The relatively few examples we identified, relative to the number of trials conducted each year, suggest the field of research is still in its early stages.

The included studies spanned many aspects of trial design. Including patients’ preferences may impact which interventions are included, which outcomes are measured, how they are measured, and how an important difference is defined. Preferences can be used to weight composite outcomes to better reflect the views of patients, which may impact the interpretation of trial results (16–18,23–31). Including patient preferences may even impact whether conducting the clinical trial is worthwhile (28). While most of the identified applications in this review were clearly linked to the potential benefit for patients, there may also be benefits to researchers. Including patient preferences in sample size calculations may identify that less participants are required (32,33). Additionally, using patient preferences may help researchers identify ways to modify trials to better suit the patients who will be participating in the trials to improve recruitment (34,35).
While the examples demonstrate the value of including preferences in trial design, challenges remain. Including patient preferences in trial design is more work, and may not always add value, incurring unwarranted delays in trial conduct. However, including preferences may lead to better research with a greater impact on patient care, and thus may be worth the additional work. Measuring preferences requires careful consideration to potential biases, including hypothetical bias (when participants report preferences that may not be true to what they would actually prefer), and scenario misspecification (if participants interpret the choice tasks differently than the researchers intended) (37). Preference heterogeneity is also a challenge, often related to contextual factors and disease severity (4,38), and can change over time (39,40), so preference elicitation should be broad enough to be reflective of the diversity in the target population of the intervention. Trials can also be tailored trials to account for these individualized preferences (22). Ultimately, while formal preference elicitation can provide quantitative information to defined problems and sample a broader group of patients than would typically be involved in the design of a trial, the results need to be interpreted carefully with these limitations in mind. Ideally, this should occur within a program of robust patient engagement in the clinical trial, as is increasingly recommended, which may include formal qualitative approaches (41,42). Indeed, qualitative work and patient involvement are also core aspects when designing preference elicitation exercises (5).

Our review focused on the application of quantitative preference elicitation methods to the design stage of clinical trials, but preferences can be considered across the evidence continuum (Figure 2). Furthermore, other approaches may be taken. For example, qualitative preference elicitation methods, such as interviews and focus groups, can allow for a deeper understanding of...
patient preferences in healthcare, and can also be used to inform trials (43,44). Our work complements several other initiatives. The United States Food and Drug Administration (FDA) has provided guidance on the value of patient preference information in regulatory decision-making and clinical trials (8). According to the FDA, patient preferences could be used to inform the design and analysis of clinical trials. They identify examples where the elicitation of patient preferences has informed the approval and decision-making process for available treatments, and postulate that patient preference information shows promise for estimating patient trade-offs when designing clinical trials (8,45). The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project aims to assess when and how patient preferences on benefits and risks should be incorporated into treatment decisions (46). Through PREFER, a multitude of preference studies have been conducted across chronic conditions, with consideration to the inclusion of patient preferences in the process of clinical trials and drug development, from pre-approval of treatments to post-authorization(46–48). Both the FDA and PREFER have highlighted the promise and potential value of including patient preferences when designing clinical trials. This has been echoed by OMERACT (Outcome Measures in Rheumatology), an international organization committed to outcome measurement in rheumatology, which has recently established a working group to develop guidance on best practices for incorporating patient preferences within clinical trials (49,50). This scoping review will help inform these efforts by providing an inventory of concrete examples of how patient preferences can be used in the design of clinical trials.

Our review is unique in that we focused on trial design rather than the analysis, dissemination, or interpretation stages. Including patient preferences in the design stage is important because it will
Scoping review on preferences and trials

influence the rest of the trial, and subsequently the evidence generated from trials. We
considered applications across health conditions. We followed rigorous scoping review
methodology, and our protocol incorporated feedback from the research team with expertise in
knowledge synthesis and the conduct of reviews. There are limitations. Our supplementary
search strategy was limited to articles in English from 2010-present and did not include grey
literature or unpublished registered trials. Data were extracted by one reviewer, although was
checked by another and discussed with the research team. We may have missed studies with
relevant applications to trial design if not explicitly stated by the authors. Further, many
preference elicitation studies could help inform clinical trial decisions, even if this was not the
intention of the authors. Our results should not be viewed as an exhaustive list of the potential
applications of preference elicitation methods for trial design, although we were able to identify
18 studies with detailed and relevant applications to various aspects of clinical trial design.
Finally, while we focused on quantitative preference elicitation methods that ask participants to
make an explicit choice related to treatment interventions, other approaches can be used to
inform clinical trial design. Overall, this review identifies examples of quantitative ways that
patient preferences are beginning to be used in clinical trial design, which may have the potential
to benefit both patients and researchers.

5. Conclusion

Using a scoping review, we identified examples of how preference elicitation methods have been
applied to the design of clinical trials across chronic health conditions. Though often used to
evaluate existing evidence, it is not yet common practice to use patient preferences to inform
clinical trial design. Our findings indicate several ways that patient preferences can help inform
Scoping review on preferences and trials

trial design and complement existing efforts to address patient priorities in clinical trials. Overall, the use of preference elicitation methods for trial design is novel, however many unanswered questions remain, and these challenges need to be addressed to help realize the potential of including preferences to inform trial design. Future work with a broader group of stakeholders is needed to understand best practices, as well as the barriers and facilitators of using preference elicitation methods for clinical trial design.

DECLARATIONS

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Specific author contributions: Planning and conducting the study (MT, GS), data collection (MT, DK), data interpretation (MT, GS, DM), drafting the manuscript (all authors). All authors have approved the final draft submitted.

Writing Assistance: None

REFERENCES

Scoping review on preferences and trials


Scoping review on preferences and trials


Scoping review on preferences and trials


Scoping review on preferences and trials

Table captions

Table 1. Study characteristics

Table 2. Preference elicitation methods used in included studies

Figure captions

Figure 1. PRISMA diagram

Figure 2. Some potential applications of preference elicitation methods to clinical trials
Table 1. Study Characteristics

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Health condition</th>
<th>Preference elicitation method used (see Table 2)</th>
<th>Application to trials</th>
<th>Stated purpose of using preference elicitation method</th>
</tr>
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<tbody>
<tr>
<td>SPIRIT checklist item 6b. Background and rationale: Choice of comparators</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Morgan et al. 2018 (20)</td>
<td>UK</td>
<td>Smoking cessation in pregnancy</td>
<td>DCE</td>
<td>Intervention selection</td>
<td>To understand incentive mechanisms of action for smoking cessation in pregnancy and breastfeeding, develop a taxonomy and identify promising, acceptable, and feasible interventions</td>
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<tr>
<td>SPIRIT checklist item 8. Trial design</td>
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<td></td>
<td></td>
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<td>Cheung et al. 2020 (21)</td>
<td>England</td>
<td>Chronic diseases</td>
<td>DCE</td>
<td>Trial design</td>
<td>To describe individual patient preferences for Personalized Trials and to identify factors and conditions associated with patient preferences.</td>
</tr>
<tr>
<td>SPIRIT checklist item 12. Outcomes</td>
<td>Fraenkel et al. 2021(16)</td>
<td>USA</td>
<td>Rheumatoid arthritis</td>
<td>Trajectory mapping</td>
<td>Prioritizing outcomes</td>
</tr>
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<tr>
<td>Herzog et al. 2014 (22)</td>
<td>USA</td>
<td>Ovarian cancer</td>
<td>Trade-off survey</td>
<td>Prioritizing outcomes</td>
<td>To determine appropriate clinical trials endpoints in ovarian cancer and which endpoints cancer patients find relevant.</td>
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<td>Stamuli et al. 2017 (23)</td>
<td>England</td>
<td>Rheumatoid arthritis</td>
<td>DCE</td>
<td>Prioritizing outcomes</td>
<td>To establish the preferences of people with rheumatoid arthritis about the best outcome measure for a health and fitness intervention randomized controlled trial.</td>
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<td>Authors</td>
<td>Country</td>
<td>Disease</td>
<td>Method</td>
<td>Composite outcomes</td>
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<td>Ahmad et al.</td>
<td>Netherlands</td>
<td>Cardiovascular</td>
<td>VAS</td>
<td>Weighting composite outcomes</td>
<td>To determine the relative importance clinicians and patients place on each of the individual components of a composite outcome (Major Adverse Cardiovascular Events; MACE).</td>
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<tr>
<td>Butler et al.</td>
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<td>Schizophrenia</td>
<td>Simple stated preference</td>
<td>Weighting composite outcomes</td>
<td>To develop individualized composite outcomes for patients based on preferences.</td>
</tr>
<tr>
<td>Haac et al.</td>
<td>USA</td>
<td>Venous thromboembolism in orthopaedic trauma patients</td>
<td>DCE</td>
<td>Weighting composite outcomes</td>
<td>To use a patient-centered weighted composite outcome to globally evaluate aspirin versus low-molecular-weight heparin for venous thromboembolism prevention in fracture patients.</td>
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<td>Metcalfe et al. 2020 (17)</td>
<td>Canada</td>
<td>Pregnancy hypertension</td>
<td>BWS Case 2 Weighting composite outcomes</td>
<td>To explore women’s treatment priorities, treatment preferences, and decisional needs for the management of pregnancy hypertension.</td>
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<td>Stafinski et al. 2015 (27)</td>
<td>USA</td>
<td>Cardiovascular</td>
<td>Rating, ranking, point-allocation, and trade-off surveys</td>
<td>Weighting composite outcomes</td>
<td>To elicit patients' perceptions of the importance of cardiovascular outcomes and treatment complications and compare them with those of clinicians.</td>
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<td>USA</td>
<td>Cardiovascular</td>
<td>Constant sum Weighting composite outcomes</td>
<td>To determine whether the relative importance of each individual end point within the composite endpoint may differ between patients and researchers.</td>
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<td>Study Authors</td>
<td>Country</td>
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<td>Coronary revascularization</td>
<td>DCE</td>
<td>Weighting</td>
<td>To describe the relative importance of major adverse cardiac and cerebrovascular events (MACCE) elements from a patient perspective.</td>
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<tr>
<td>Vaanholt et al. 2018 (29)</td>
<td>England</td>
<td>Coronary artery disease</td>
<td>DCE</td>
<td>Weighting</td>
<td>To examine patients' perspectives regarding composite endpoints and the utility patients put on possible adverse outcomes of revascularization procedures.</td>
</tr>
<tr>
<td>Chaisinanunkul et al. 2015 (30)</td>
<td>USA</td>
<td>Acute stroke</td>
<td>TTO</td>
<td>Developing</td>
<td>To weight the 7 modified Rankin Scale (mRS) levels by utilities in order to improve scale interpretability while preserving statistical power.</td>
</tr>
</tbody>
</table>

SPIRIT checklist item 14. Sample size
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Condition</th>
<th>Methodology</th>
<th>Sample size</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franco et al.</td>
<td>England</td>
<td>Fall prevention in older adults</td>
<td>DCE</td>
<td>Sample size</td>
<td>To estimate the smallest worthwhile effect (SWE) of exercise programs designed to prevent falls among older people and to compare estimates derived by two methodological approaches.</td>
</tr>
<tr>
<td>Chaudhuri et al.</td>
<td>England</td>
<td>Obesity</td>
<td>DCE</td>
<td>Sample size</td>
<td>To calculate acceptable levels of uncertainty (significance level and power) when designing clinical trials by using preference-weights to calculate Type I and II errors.</td>
</tr>
<tr>
<td>SPIRIT checklist item 15. Recruitment</td>
<td>Kerman et al.</td>
<td>Netherlands</td>
<td>Osteoarthritis</td>
<td>Recruitment</td>
<td>To estimate the proportion of potentially eligible subjects who would be willing to participate in</td>
</tr>
</tbody>
</table>
Smith et al. 2016 (34)  USA  Chronic pain  Adaptive choice-based conjoint analysis  Recruitment  To assess characteristics that may affect enrollment in pharmacologic pain treatment trials.
<table>
<thead>
<tr>
<th>Preference elicitation methods used by included studies</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best worst scaling (BWS)</td>
<td>Case 1 presents items with no attributes or level structure and asks participants to choose the best and worst statements that compete with one another so that multiple items cannot be considered equally important (11). In Case 2 participants are asked to choose the best and worst attributes and levels within a single profile. In Case 3 participants are asked to choose the best and worst attributes and levels across multiple profiles, i.e., the participant chooses the best and worst profiles. In our included studies, only Case 2 was identified*.</td>
</tr>
<tr>
<td>Conjoint analysis (CA)</td>
<td>Conjoint analysis (CA): A broad set of methods that are used to measure preferences and trade-offs. Uses preferences to derive the implicit values for an attribute of an intervention from an overall profile score comprised of two or more attributes (5). Adaptive choice-based conjoint analysis (ACBC): A type of CA where choice tasks are customized to the participant based on the attributes they choose (34). Participants must complete a Build-Your-Own exercise to select their preferred attributes and levels. Participants then complete a screening task showing partial profiles to identify trade-offs, followed by a complete a set of</td>
</tr>
</tbody>
</table>
choice tasks, which are used to estimate the value participants place on each attribute.

<table>
<thead>
<tr>
<th>Discrete choice experiment (DCE): A stated preference method asking participants to choose between a set of alternatives. Participants are presented with a choice of 2 or more treatments with different attributes. The value participants place on each attribute is estimated, under the assumption that participants will choose the treatment with the highest overall value to them (2,4). A DCE is a specific form of conjoint analysis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant sum</td>
</tr>
<tr>
<td>Simple stated preference</td>
</tr>
<tr>
<td>Time trade-off (TTO)</td>
</tr>
<tr>
<td>Trajectory mapping</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Visual analogue scale (VAS)</td>
</tr>
</tbody>
</table>

*Indicates non-traditional preference elicitation methods that were included because they weighted attributes with the intention of informing clinical trial design.
Figure 1. PRISMA Diagram

Initial Search of Reviews

- Records identified through MEDLINE (no time limit) \( n=2648 \)

- Records identified through EMBASE (no time limit) \( n=732 \)

- Records after duplicates removed \( n=5419 \)

- Records screened \( n=5419 \)

- Records excluded \( n=5289 \)

- Full text records identified for assessment \( n=130 \)

- Full text records \( n=95 \)

- Full text records assessed \( n=33 \) (947 primary studies)

- Records not extracted \( n=62 \)

- Primary studies included in synthesis \( n=2 \)

Search of Primary Studies

- Records identified through MEDLINE (2010-) \( n=5435 \)

- Records after duplicates removed \( n=5419 \)

- Records screened \( n=5419 \)

- Records excluded \( n=5330 \)

- Full text records identified for assessment \( n=89 \)

- Full text records \( n=595 \)

- Full text records assessed \( n=33 \) (947 primary studies)

- Records not extracted \( n=62 \)

- Primary studies included in synthesis (supplementary + hand searched) \( n=13+3 \)

- Primary studies included in synthesis \( n=18 \)
Figure 2. Some potential applications of preference elicitation methods to clinical trials

Scope of review

- Design
  - Selecting comparators
  - Selecting outcomes
  - Defining eligibility criteria
  - Informing worthwhile effect sizes and sample size calculations

- Conduct
  - Allocating patients to their preferred treatment arm (preference trials)
  - Monitoring preferences alongside trial

- Analysis
  - Understanding patient preferences
  - Exploring preference heterogeneity and its impact on interpretation of results
  - Determining a worthwhile effect

- Interpretation
  - Informing shared decision-making approaches
  - Economic evaluation and resource allocation
The application of preference-based methods in clinical trial design to quantify trade-offs: A scoping review

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Affiliations: 1 Department of Community Health Sciences, University of Calgary, Calgary, Alberta; 2 Department of Medicine, University of Calgary, Calgary, Alberta; 3 Department of Medicine, McGill University, Montreal, Quebec; 4 Centre for Outcomes Research & Evaluation, Research Institute McGill University Health Centre; 5 Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta

Correspondence: Dr. Glen Hazlewood, Department of Medicine and Department of Community Health Sciences, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, T2N 4N1, Canada. gshazlew@ucalgary.ca

Journal: The Patient: Patient-Centered Outcomes Research

Supplementary materials: Search strategy
Search strategies

MEDLINE Search Strategy (Initial Search of Reviews)

1. conjoint analysis.tw,kf.
2. discrete choice experiment*.tw,kf.
3. rating task*.tw,kf.
4. ranking task*.tw,kf.
5. choice experiment*.tw,kf.
6. risk attitude*.tw,kf.
7. risk aversion.tw,kf.
8. discrete choice*.tw,kf.
9. standard gamble.tw,kf.
10. willingness to pay.tw,kf.
11. willingness-to-pay.tw,kf.
12. decision support technique*.tw,kf.
13. decision support system*.tw,kf.
14. time trade*.tw,kf.
15. trade off*.tw,kf.
16. stated preference*.tw,kf.
17. contingent valuation.tw,kf.
18. choice experiment.tw,kf.
19. exp Health Priorities/
20. choice behavio*.tw,kf.
21. patient consensus.tw,kf.
22. Part-worth utility*.tw,kf
23. discrete choice*.tw,kf.
24. ((patient$ or participant$) adj3 (preference$ or choice$ or value$ or priorit$)).tw,kf.
25. Paired comparison.tw,kf.
27. Conjoint measurement.tw,kf.
29. or/1-28
30. systematic review.pt
31. scoping review*.tw,kf
32. scoping-review*.tw,kf
33. systematic review.*tw,kf
34. systematic overview*.tw,kf
35. quantitative review*.tw,kf
36. quantitative overview*.tw,kf
37. quantitative syntheses*.tw,kf
EMBASE Search Strategy (Initial Search of Reviews)

1. discrete choice experiment*.ti,ab,kw.
2. rating task*.ti,ab,kw.
3. ranking task*.ti,ab,kw.
4. choice experiment*.ti,ab,kw.
5. risk attitude*.ti,ab,kw.
6. risk aversion.ti,ab,kw.
7. discrete choice*.ti,ab,kw.
8. standard gamble.ti,ab,kw.
9. willingness to pay.ti,ab,kw.
10. willingness-to-pay.ti,ab,kw.
11. decision support technique*.ti,ab,kw.
12. decision support system*.ti,ab,kw.
13. time trade*.ti,ab,kw.
14. trade off*.ti,ab,kw.
15. stated preference*.ti,ab,kw.
16. contingent valuation.ti,ab,kw.
17. choice experiment.ti,ab,kw.
18. exp Health Priorities/
19. choice behavio*.ti,ab,kw.
20. patient consensus.ti,ab,kw.
22. discrete choice*.ti,ab,kw.
(patient* or participant$) adj3 (preference* or choice* or value* or priorit*)
Paired comparison
Pairwise choice
Conjoint measurement
Conjoint stud*
28. or/1-28
systematic review*
scoping review*
scoping-review*
systematic overview*
quantitative review*
quantitative overview*
quantitative synthesis*
research integration*
research overview*
integrative review*
collaborative review*
collaborative overview*
data synthesis*
data extraction*
data abstraction*
handsearch*
hand search*
29 and 48
(systematic review* or scoping review*) not exp human/
50. 49 not 50

MEDLINE Search Strategy (Primary Studies)

1. conjoint analysis.tw,kf.
discrete choice experiment*.tw,kf.
3. rating task*.tw,kf.
4. ranking task*.tw,kf.
5. choice experiment*.tw,kf.
6. risk attitude*.tw,kf.
7. risk aversion.tw,kf.
discrete choice*.tw,kf.
standard gamble.tw,kf.
time trade*.tw,kf.
11. stated preference*.tw,kf.
12. contingent valuation.tw,kf.
13. choice experiment.tw,kf.
14. patient consensus.tw,kf.
16. ((patient$ or participant$) adj2 (preference$ or choice$ or value$)).tw,kf.
17. Paired comparison.tw,kf.
18. Pairwise choice.tw,kf.
19. Conjoint measurement.tw,kf.
21. or/1-20
22. exp animals/ not humans.sh.
23. 21 not 22
24. trial*.tw,kf.
25. outcome selection.tw,kf.
26. composite outcome*.tw,kf.
27. important difference*.tw,kf.
28. minimal clinically important difference*.tw,kf.
29. non-inferiority margin*.tw,kf.
30. intervention selection.tw,kf.
31. trial priorit*.tw,kf.
32. end-point selection.tw,kf.
33. outcome measure*.tw,kf.
34. composite end point*.tw,kf.
35. or/24-34
36. MCID.tw,kf.
37. CID.tw,kf.
38. 36 or 37
39. 35 or 38
40. 39 not 22
41. 23 and 40
42. limit 41 to yr="2010 -Current"