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ORIGINAL RESEARCH

Content Validity of the Hemophilia Device Handling and Preference Assessment Questionnaire - A Cognitive Debrief Study in Patients with Hemophilia and Their Caregivers

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Introduction: As new treatment options using different modes of administration become available for patients with hemophilia, it is important to assess how patients and caregivers perceive the use of different injection systems.

Aim: This study aimed to evaluate patient comprehension, relevance, and comprehensiveness of the *Hemophilia Device Handling and Preference Assessment* (HDHPA) instrument among the hemophilia population. Specifically, cognitive interviews were to be conducted to establish evidence of the content validity for the instrument's use in a handling and preference study.

Methods: This cross-sectional interview study included participants randomly selected from a pen-injector handling and preference study in the USA who had self-administered a ten-item HDHPA questionnaire. Subsequently, semi-structured cognitive interviews were conducted examining HDHPA instrument instructions, items, and response options.

Results: The study sample consisted of 20 participants (50% adult patients, 25% adolescents, and 25% caregivers; 75% male). Most participants (89–100%) demonstrated comprehension of the instructions given. Nearly all participants (94–100%) demonstrated clear comprehension of the ten HDHPA items. All 20 participants stated that the questionnaire was relevant and comprehensive in assessing the pen-injector and comparing it to their current device.

Conclusion: The results of this study showed that the HDHPA items are comprehensible, relevant, and comprehensive, thereby confirming the content validity of this instrument.

Keywords: hemophilia, questionnaire design, patient preference, content validity, patient experience

Introduction

Hemophilia A and B (HA and HB) are rare, inherited bleeding disorders in which a lack of clotting factors can lead to spontaneous bleeding, as well as longer bleeding times following surgery or injury.[1,2] The current standard of care for hemophilia involves either factor replacement therapies that are administered intravenously or non-factor therapies that can be given subcutaneously.[3] Prophylactic treatment is recommended for patients with severe hemophilia and requires regular injections.[4]

Vial and syringe injection systems currently used for both intravenous and subcutaneous administration have been reported to be error-prone and can impose a high treatment burden and dependency of younger patients on caregivers.[5] In recent years, pen-injectors have been developed to counteract challenges associated with treatment administration. In diabetes, where pen-injectors are widely used, increased ease of use and improved patient adherence to treatment have been observed.[6,7]

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Pen-injectors for hemophilia treatment delivery are currently under development.[8] One of them is the DV3356 pen-injector, a multiple-dose, disposable, prefilled device using a 4 mm long, single-use, disposable NovoFine® Plus 32G (0.23 mm/0.25 mm) needle. The pen-injector is intended for subcutaneous delivery of concizumab, a recombinant monoclonal antibody for the treatment of HA and HB, currently approved by the European Medicines Agency and the U. S. Food and Drug Administration for once-daily, subcutaneous prophylaxis in HA and HB with inhibitors.[9–11] Concizumab targets the tissue factor pathway inhibitor, thereby enhancing thrombin generation via increased factor Xa production.

To date, hemophilia patients' perceptions of the risks associated with the use of a pen-injector have not been assessed. Therefore, there is a need for a tool that captures potential risks of misapplication and patients' preferences regarding the attributes of injection systems. Insights into patients' preferences may better guide the development of current and future injection devices and improve ease of use and treatment adherence.[12,13] In turn, adherence to prophylactic treatment can reduce bleeding events in patients with hemophilia and improve quality of life.[14–16]

The *Hemophilia Device Handling and Preference Assessment* (HDHPA) questionnaire is an instrument that can be used to assess how learning to use and actually using various injection systems are perceived among patients with hemophilia and their caregivers. The HDHPA is based on similar tools that have been used to assess device preference in other conditions.[17,18] The appropriateness of the HDHPA instrument as a self-reported assessment of participants' use of and experience with injection systems has not been evaluated to date and needs to be established. We present results from a handling and preference study that used cognitive interviews to establish the content validity of the HDHPA and to evaluate whether its items are comprehensible, relevant, and comprehensive.

Material and Methods

Study Design and Participants

This cross-sectional study aimed to build evidence towards determining whether the HDHPA instrument is appropriate as a tool for self-reported assessment of the use of, and experience with, an injection device. Participants were randomly selected from a handling and preference study, fielded in five locations in the United States evaluating a pen-injector intended for concizumab delivery.[19] Participant selection had to meet the following criteria: ten adult hemophilia patients, five adolescent patients, and five caregivers from within this population. The study followed the FDA's 2009 Patient-Reported Outcome (PRO) Guidance for Industry,[20] FDA's Patient-Focused Drug Development guidance documents 3 and 4,[21] and current scientific best practices for conducting cognitive debriefing interviews as part of instrument development.[20–22]

The handling and preference study, as well as the cognitive interviews, were conducted by Research Collective LLC (Tempe, AZ, USA) sponsored by Novo Nordisk A/S (Søborg, Denmark), the latter in collaboration with OPEN Health (Bethesda, MD, USA), sponsored by Novo Nordisk Inc. (Plainsboro, NJ, USA). The study received ethical approval from Castle IRB (Chesterfield, MO, USA) and was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations. All participants or, for patients under 18 years of age, parents or legal guardians, provided informed consent.

Eligible participants for the interview study included adult (≥18 years) and adolescent (10–17 years) patients with hemophilia, and adult caregivers of patients with hemophilia. Inclusion and exclusion criteria have been previously described.[19] All participants were compensated for their time after the completion of the interview.

Interview Process

The flow of participants who took part in the handling and preference study before their involvement in the cognitive interviews is shown in Figure 1. As part of the handling and preference study, participant demographics and clinical characteristics, including age, gender, hemophilia type, and length of hemophilia treatment were assessed.[19] Participants then self-administered the HDHPA questionnaire. The questionnaire consists of ten items that assess concepts, including device ease of use, device confidence, and device preference.[19]

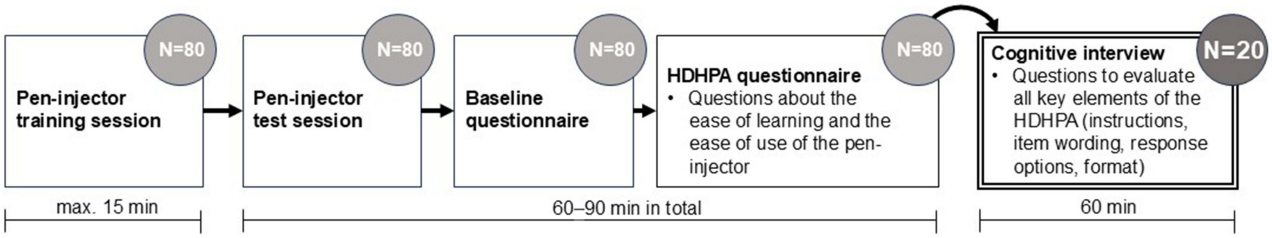

Figure 1 Flowchart of study design and implementation. Tiles 1–4 show the study flow of a handling and preference study using the HDHPA questionnaire, the results of which have been previously published.[19] Tile 5 shows the cognitive interview, the results of which are reported here.
Abbreviation: HDHPA, Hemophilia Device Handling and Preference Assessment.

One-on-one cognitive interviews were conducted directly after the HDHPA, using a semi-structured interview guide (Supplementary information 1). Each interview included an explanation of the purpose and process of the interview, and a "think-aloud" debrief[22] on the ten HDHPA items in which participants were asked to verbalize the thought process they used when reading and responding to each item. Follow-up probes were used to evaluate the comprehension, relevance, and comprehensiveness of the HDHPA content and instructions (Supplementary information 1).

Interviews were conducted face-to-face and lasted approximately 60 minutes. All interviews were recorded and transcribed. The first nine participants constituted wave 1 and the subsequent participants constituted wave 2. As a result of pre-planned reflection and review between waves 1 and 2, changes were made to the interview guide (one follow-up probe was added and one removed), and a typographical error was corrected within the HDHPA to streamline the interview and reduce burden on subsequent participants.

Data Analysis

Participant demographic and clinical information and their ranking results were managed in Microsoft® (MS) Excel® with descriptive statistics generated (count, percentage, mean, median, and standard deviation [SD]).

The interviews were analyzed by first organizing verbatim patient responses to each structured probe question for each evaluated HDHPA item. Interview transcripts and interviewers' notes were tabulated to organize and present relevant verbatim patient responses related to each HDHPA item, the number of participants demonstrating comprehension, and confirming the relevance of the item content. In addition, any difficulties noted when navigating the question (stated directly by the participant or observed by the interviewer) were documented, and the rationale for any potential revisions to the target instrument or interview approach was highlighted within the tables.

Results

Participant Characteristics

Twenty participants took part in the cognitive interview study, with an average age of 29.4 years (range 12–66; 50% of participants were adult patients, 25% were adolescent patients, and 25% were caregivers); participants were predominantly male (75%). The participant characteristics are summarized in Table 1. Most patients (including patients self-reporting and caregivers reporting for their patients) had HA without inhibitors (80%) and had been treated for hemophilia for an average time of 18.3 years (range 9–46).

HDHPA: Comprehension of Instructions

All respondents (n=17/17; 100% [3 answers not reported]) demonstrated comprehension of the instructions related to items 1–4 and items 9+10. Most respondents (n=16/18; 89% [2 answers not reported]) demonstrated comprehension of the instructions related to items 5–8. Two participants had challenges with the word "prophylactic" and needed clarification.

Table 1 Participant Demographics and Clinical Characteristics

Characteristics		Participants (N=20)
Age (Years)	Mean (SD)	29.4 (13.5)
	Median	30.0
	Range	12-66
Gender, n (%)	Male	15 (75)
	Female	5 (25)
Types of participants interviewed, n (%)	Adult patient with hemophilia	10 (50)
	Adolescent patient with hemophilia	5 (25)
	Caregiver of hemophilia patient	5 (25)
Highest level of education completed, n (%)	Middle school	3 (15)
	Some high school	2 (10)
	High school graduate/GED	6 (30)
	Some college/technical school	4 (20)
	College graduate	3 (15)
	Advanced	2 (10)
Type of hemophilia[a], n (%)	Hemophilia A without inhibitors	16 (80)
	Hemophilia B without inhibitors	4 (20)
Length of hemophilia treatment (Years)[a,b]	Mean (SD)	18.3 (10.5)
	Median	13.0
	Range	9-46

Notes: [a]For type of hemophilia and length of hemophilia treatment, responses from caregiver participants reflect the characteristics of the patients that they care for. [b]Rather than a specific number, participant A17 reported "a few years" for treatment duration and has been excluded from the calculation of the average duration.
Abbreviations: GED, General Equivalency Diploma; SD, standard deviation.

HDHPA: Comprehension of Item Text and Response Options

Overall, almost all responding participants demonstrated clear comprehension of items 1–10 in the HDHPA. One participant expressed some difficulty with understanding the text of item 1a, and suggested that amending the text from "learn how to use the pen-injector" to "learn how to prepare the pen-injector" would make the item clearer. A detailed breakdown of each evaluated item with corresponding responses related to interpretation or comprehension is presented in Table 2. Participants either described no difficulty choosing an option for all items, and/or were able to provide clear examples showing the distinction between each level for the HDHPA items.

HDHPA: Relevance of Assessed Concepts

All 20 participants stated that the questionnaire was relevant to their experience of using a pen-injector. For example, one participant noted that, "I think it did a good job." Another participant found that, "I think this is extremely important." Full responses to this question are provided in Supplementary Table 1.

Table 2 Comprehension of Item Text of HDHPA

Item[a]	Percentage of Participants Demonstrating Comprehension of Item[b,c]	Percentage of Participants Reporting No Difficulty Selecting a Response	Responses Related to Difficulty with Comprehension of Item or Selecting a Response
Item 1a (Learning use)	94% (17/18)	100% (18/18)	Difficulty with comprehension "Maybe learn how to prepare the pen-injector instead of use." (Q: "OK, how to prepare the pen-injector would be more clear?") A: "Mm-hmm" [to indicate yes].
Item 1b (Preparing for injection)	100% (20/20)	100% (20/20)	N/A
Item 1c (Selecting dose)	100% (19/19)	100% (20/20)	
Item 1d (Injecting dose)	100% (20/20)	100% (20/20)	
Item 1e (Portability)	100% (20/20)	100% (20/20)	
Item 1f (Using outside home)	100% (20/20)	100% (20/20)	
Item 1g (Storage)	100% (20/20)	100% (19/19)	
Item 1h (Disposal)	100% (20/20)	100% (20/20)	
Item 2 (Level of difficulty)	100% (20/20)	100% (20/20)	
Item 3a (Correct use)	100% (20/20)	100% (20/20)	
Item 3b (Full dose)	100% (18/18)	100% (19/19)	
Item 4 (Speed of administration)	100% (20/20)	100% (20/20)	
Item 5a (Compare learning use)	100% (18/18)	100% (19/19)	
Item 5b (Compare preparing for injection)	100% (18/18)	100% (18/18)	
Item 5c (Compare selecting dose)	100% (18/18)	100% (17/17)	
Item 5d (Compare injecting dose)	100% (18/18)	100% (18/18)	
Item 5e (Compare portability)	100% (18/18)	100% (17/17)	
Item 5f (Compare using outside home)	100% (17/17)	100% (17/17)	
Item 5g (Compare storage)	100% (18/18)	100% (18/18)	
Item 5h (Compare disposal)	100% (18/18)	100% (18/18)	
Item 6 (Compare level of difficulty)	100% (17/17)	100% (18/18)	

(*Continued*)

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Table 2 (Continued).

Item[a]	Percentage of Participants Demonstrating Comprehension of Item[b,c]	Percentage of Participants Reporting No Difficulty Selecting a Response	Responses Related to Difficulty with Comprehension of Item or Selecting a Response
Item 7a (Compare correct use)	100% (19/19)	100% (18/18)	
Item 7b (Compare full dose)	100% (17/17)	100% (19/19)	
Item 8 (Compare speed of administration)	100% (17/17)	100% (19/19)	
Item 9 (Preference)	100% (13/13)	100% (20/20)	
Item 10 (Strength of preference)	100% (19/19)	100% (18/18)	

Notes: [a]Item questions can be cross-checked against the HDHPA questionnaire provided in the Supplementary materials. [b]The denominator in this table represents the total number of participants providing a response for that item and may not be equal to the full study sample for some items. [c]For the purposes of this summary, comprehension of item content was defined as: 1) Participant expressing the meaning as intended when asked "What is the item asking you, in your own words" and/or 2) Participant expressing that they had no difficulty when asked "Did you have any difficulty understanding the item?".

HDHPA: Importance of Item Content – Ranking Exercise and Summary Questions

To better understand the relevance and importance of the eight device-related activities explored in items 1a-h (learning to use, preparation, dose selection, dose injection, portability, use outside the home, storage, and disposal), participants were asked to rank the importance of the activities on a scale from 1 to 8, where 1 was the most important and 8 the least important. Of the activities, the top 3 were "injecting the dose", "learning how to use the pen-injector", and "selecting the correct dose"; the activity ranked as the least important was "disposing of the pen-injector". Figure 2 summarizes the proportions of participants ranking each activity from 1 to 8.

When asked which questions of the HDHPA addressed the most important and least important aspects in determining whether the pen-injector is easy to use, the responses were largely aligned with those seen in the ranking exercise.

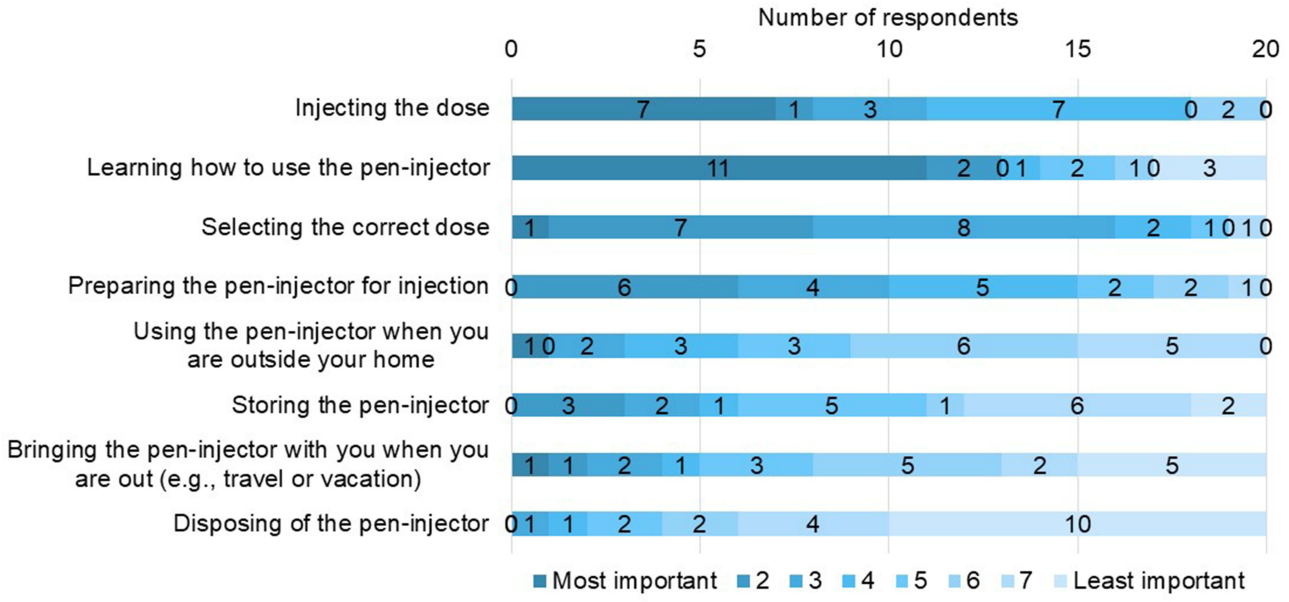

Figure 2 Activity importance rankings. The importance ranking of the eight device-related activities was explored in item 1 (learning to use, preparation, dose selection, dose injection, portability, use outside the home, storage, and disposal) on a scale from 1 to 8, where 1 is the most important and 8 is the least important.

"Learning how to use the pen-injector", "selecting the correct dose", "injecting the dose", and "preparing the pen-injector for injection" were the aspects that participants considered as most important when evaluating ease of use of a pen-injector, while "storing" and "disposing" were considered by participants as the least important aspects. The full responses to this question are summarized in Supplementary Table 2.

HDHPA: Overall Assessment – Comprehensiveness and Comprehension

Participants were also asked to provide their overall assessment of the HDHPA, focusing on comprehensiveness, especially when comparing the pen-injector to their current device and difficult terms that affected their comprehension of the instrument. Most participants considered the HDHPA to be comprehensive and did not note any missing concepts that were relevant for the comparison of the pen-injector with their current device. Although some additional aspects were raised by the participants, none were raised by more than one participant (Supplementary Table 3). Most participants responded very positively to the HDHPA and did not raise any difficult terms or required clarifications. Only one issue was raised by more than one participant, where two participants expressed their challenge with the term "prophylactic". Additionally, some suggestions related to the wording and design of the questionnaire were made by individual participants. These suggestions include providing examples for storing, differentiating between pen-injector and needles, providing bolding to highlight the phrases "preparing" and "injecting", offering visuals to items 1a and 1g, and using the term "throwing it away" rather than "disposing". Full responses to this question are provided in Supplementary Table 3.

Discussion

This is the first study to examine the content validity of a hemophilia-specific tool for assessing patients' and caregivers' device handling experience and preference, focusing on prophylactic treatment injection systems. Using interviews and analytical methods suitable for the evaluation of content validity in PRO tools,[20,23] the findings establish evidence of the comprehension, relevance, and comprehensiveness of HDHPA content among patients and caregivers. In line with accepted practices for cognitive interviewing, a sample size of 20 participants was established to be sufficient to identify common themes and problematic survey items.[22]

Most participants reported that the instructions, response options, and concepts assessed by the HDHPA items were comprehensible and relevant. Two participants expressed difficulty in understanding the term "prophylactic" in the instructions prior to item 5 (asking participants to compare their experience with the pen-injector with their currently used device), leading to the addition of an explanatory sentence in the HDHPA.

Current injection systems using the vial and syringe method pose several challenges, including inconvenient administration and application errors, which in hemophilia may lead to life-threatening situations.[5,19] There is a high unmet need among hemophilia patients and caregivers for easier and quicker administration methods, which may be addressed by pen-injectors. In diabetes, pen-injectors are regarded as accurate and convenient, and are associated with high treatment adherence.[7,24] It is important to develop and validate assessment tools for new injection systems in hemophilia that allow understanding of patient experience and the potential risks for misapplication.

Multiple validated tools are available to evaluate the overall patient preference for treatment.[25–27] However, there is a need for tools specifically evaluating device attributes and comparing different injection systems for the administration of hemophilia therapies. The HDHPA instrument is designed to meet this need; however, it has not yet been formally validated. Notably, the domains assessed within the HDHPA, such as ease of use and experience with the device, align with those assessed in previous device studies in this area, as well as in device studies in diabetes.[28–32]

The HDHPA was used in a study assessing handling and preference of a pen-injector for the administration of the anti-tissue factor pathway inhibitor (TFPI) concizumab in comparison with currently used injection systems. A very high proportion of patients (98%, n=78/80) found the device "easy" or "very easy" to use, and "easier" or "much easier" (96%, n=77/80) to use than their existing device.[33] Patients who agree with their treatment and administration method are likely to be more compliant and may consequently improve their overall health outcome. Therefore, the ability to assess patients' handling and preference with respect to their injection system with a validated tool is an important aspect when developing and introducing new injection systems.

Strengths of the present study include alignment with methodological best practices, including the FDA's PRO Guidance for Industry,[20] the FDA's guidance on Patient-Focused Drug Development, and guidance on the use of cognitive interview research.[20,25] Potential recall bias was minimized by conducting the HDHPA and the cognitive interviews immediately after each other. However, conduct of the study only in the US may limit its generalizability. The sample size was comparable to that of other cognitive interview studies that evaluated similar instruments.

Undertaking formal psychometric validation of the HDHPA may be valuable in the future. Subsequent studies could also investigate injection system preferences and experience in other countries and healthcare systems to better understand patient experience and reasons for choosing different treatments in different settings.

Conclusions

The results of this cognitive interview study in a sub-population of participants using the HDHPA questionnaire within a handling and preference study support the content validity of the HDHPA questionnaire. This confirms that the included items are comprehensible, relevant, and comprehensive to adult and adolescent patients with hemophilia and their caregivers. The HDHPA is the first structured tool to assess the preferences and experience of patients with hemophilia regarding pen-injectors, meeting a previously unmet need. By selecting the most appropriate device for the individual patient, patient adherence and health outcomes may be improved.

Data Sharing Statement

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in datasets in a de-identified and anonymized format. Data will be made available after research completion and approval of the product and product use in the EU and the USA. Information about data access request proposals can be found on novonordisk-trials.com.

Ethics Approval and Informed Consent

The study received ethical approval from Castle IRB (Chesterfield, MO, USA) and was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations. The study complied with the Declaration of Helsinki. All participants or, for patients under 18 years of age, parents or legal guardians, provided informed consent, including consenting to the results of their interview being published as long as their identity was kept confidential.

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Authors' Contributions

All authors made a significant contribution to this work. This included the conception, study design, execution, acquisition of data, analysis and interpretation, drafting, revising or critically reviewing the article. All authors gave final approval of the version to be published, agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

NKR, GTB, JSN and BB are full-time employees of Novo Nordisk A/S and own Novo Nordisk shares. **SS** was an employee of Novo Nordisk Inc when the study was conducted and moved to Jazz Pharmaceuticals in July 2023 while the

manuscript was in development. He owns Jazz Pharmaceuticals and Novo Nordisk stocks. **JHT** is a paid employee of OPEN Health, which has received funding from Novo Nordisk for the research detailed in this manuscript. OPEN Health received research funding for different projects from Biogen, Takeda, Otsuka, Novo Nordisk, AbbVie, Insmed, Merck, Alimentiv, Shinogi, Cleveland Clinic, Pfizer. **KMcC** is a paid employee of OPEN Health, which has received funding from Novo Nordisk for the research detailed in this manuscript. **EH** is a paid employee of Research Collective which has received funding from Novo Nordisk A/S for research detailed in this manuscript as well as consulting fees and travel support related to the research study. **MG** is a paid employee of Research Collective, which has received funding from Novo Nordisk A/S for research detailed in this manuscript. The authors report no other conflicts of interest in this work.

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