ORIGINAL RESEARCH

Improving Assessment of Adherence Behaviors and Drivers: Targeted Literature Review and Concept Elicitation Interviews in Multiple Countries and Disease Populations

Sarah Bentley[1], Elizabeth Exall[1], Lucy Morgan [ID][1], Nicolas Roche [ID][2], Kamlesh Khunti [ID][3], Rebecca Rossom[4], James Piercy[5], Rob Arbuckle [ID][1], Victoria S Higgins [ID][5]

[1]Patient-Centered Outcomes, Adelphi Values, Bollington, UK; [2]Respiratory Medicine, Cochin Hospital, APHP Centre University of Paris, Institut Cochin (UMR1016), Paris, France; [3]Diabetes Research Centre, Leicester University, Leicester, UK; [4]HealthPartners Institute, University of Minnesota Medical School, Minneapolis, MN, USA; [5]Adelphi Real World, Bollington, UK

Correspondence: Rob Arbuckle, Adelphi Values, Adelphi Mill, Grimshaw Lane, Bollington, SK10 5JB, UK, Tel +44 1625 576815, Fax +44 1625 577328, Email rob.arbuckle@adelphivalues.com

Purpose: Medication adherence is crucial for achieving clinical goals. Medication adherence drivers and behaviors were explored across multiple conditions, countries, and medication schedules/modalities to develop a conceptual model of medication adherence, which could later be used to support development of a patient-reported outcome (PRO) measure of adherence.

Patients and Methods: Targeted review of qualitative literature identified important medication adherence concepts. Fifty-seven qualitative concept elicitation interviews were conducted (USA n=21, Spain n=18, Germany n=18). Participants were prescribed medication for: hypertension (n=9), asthma (n=8), multiple myeloma (n=8), psoriasis (n=8), diabetes (n=7), depression (n=7), multiple sclerosis (n=7), and/or schizophrenia (n=6). Thematic analysis of verbatim transcripts was performed. Expert clinicians (n=3) provided input throughout.

Results: Nine qualitative articles were selected for review from 2168 screened abstracts. Forty-two medication adherence concepts were reported and grouped into 10 domains. Eight forms of medication adherence were reported during interviews, along with 27 drivers of non-adherence, all of which were incorporated into a conceptual model. Participants reported skipping medication doses (n=36/57; 63.2%) or taking medication later in the day than prescribed (n=29/57; 50.9%). Common drivers of non-adherence included forgetfulness (n=35/57; 61.4%), being out of the usual routine (n=31/57; 54.4%) and being busy (n=22/57; 38.6%). US participants were more likely to report non-adherence due to low perceived efficacy (n=6/21, 28.6%) and cost (n=5/21, 23.8%) than German (n=1/18, 5.6%; n=0/18, 0.0%) or Spanish (n=2/18, 11.1%; n=1/18, 5.6%) participants.

Conclusion: Findings highlight the diverse forms and drivers of medication non-adherence, informing the development of a comprehensive conceptual model of medication adherence. The conceptual model builds on and advances previous models of medication adherence and can be used by healthcare professionals to understand and interpret barriers to medication adherence and how best to support patients in taking their medication as intended.

Plain Language Summary:

- Medication adherence is the extent to which a patient takes their medication as prescribed. This paper describes a literature review and concept elicitation interviews to identify forms and drivers of medication adherence across a diverse sample of participants. Forms of non-adherence identified included: deviating from the prescription, skipping a dose, taking a different amount, and taking medication at a different time. Behaviours and drivers can vary by condition, treatment modality, and dosing schedule.

- This research highlights the variation in the prevalence of medication non-adherence, and the different forms and drivers of non-adherence, based on individuals' demographic and clinical characteristics. The conceptual model developed advances previous models of medication adherence and may support healthcare professionals in the management of patients and how they can be supported to take medication as intended. The research ultimately informed the development of the Adelphi Adherence Questionnaire (ADAQ[©]), a novel generic patient-reported outcome measure.

Introduction

The World Health Organization (WHO) defines medication adherence as

> the extent to which the persons' behaviour (taking medication, following a diet, and/or executing lifestyle change) corresponds with agreed recommendations from a healthcare provider.[1]

Unlike medication compliance, the term "medication adherence" implies that patients agree with the recommendations provided.[2,3] Medication adherence is essential for achieving clinical goals and outcomes, and optimizing patient care. Medication non-adherence can impact the effectiveness of treatment, which can in turn lead to increased healthcare costs, decreased patients health, and mortality.[4–7] It is estimated that up to 50% of patients with chronic conditions take their medications less than 80% of the time.[1,8] Further, approximately 20% of patients may intentionally stop taking their medication for periods at a time.[1]

There is evidence that medication adherence may be impacted by medical condition, modality of treatment, and number of prescribed medications (along with associated dosing schedules). Furthermore, socio-economic, demographic, geographic, and cultural population characteristics have been found to affect medication adherence.[9] Medication non-adherence has been found to be greater for chronic conditions when compared to acute conditions since patients with acute conditions may be symptom-free or less likely to experience unpleasant symptoms when medication is missed.[4] Further evidence to understand the drivers for medication non-adherence may support healthcare professionals (HCPs) to plan for and mitigate against non-adherence, leading to better patient care and outcomes.

Medication non-adherence may include taking a different amount of medication than prescribed, skipping a dose of medication, and taking medication at a different time of day than prescribed.[1] Research suggests that some forms of medication non-adherence may be unintentional with individuals simply forgetting to take medication as prescribed. Forgetting to take medication may be associated with individuals not feel unwell, being busy, or not considering their medication to be important.[9–14] Conversely, medication non-adherence may be intentional due to fear of experiencing medication side effects, perceiving that medication is ineffective, or being discouraged from taking medication by family and/or friends.[9–13,15–18]

While there is extensive published literature exploring adherence behaviors, much of the existing research focuses on specific conditions and/or treatment modalities or on just one country/culture. This highlights the need to conduct robust research in clinical and demographically diverse samples, to determine common facilitators/barriers to adherence across conditions and sociodemographic groups. In order to address this research need, this study aimed to build on existing research (identified through a review of the literature) regarding medication adherence behaviors, by conducting prospective qualitative research with individuals with varied demographic and clinical characteristics to identify and explore medication adherence forms and drivers.

Specifically, this study aimed to (1) identify and summarize concepts reported in key qualitative publications related to patients' experiences and perceptions of medication adherence and (2) conduct qualitative interviews to explore medication adherence drivers and behaviors in a diverse sample. Both of these activities were performed to support the development of a comprehensive conceptual model of medication adherence applicable across countries, conditions and treatment types.

Methodology

This study was non-interventional and included a literature review and qualitative, concept elicitation interviews which aimed to explore behaviors and drivers of medication non-adherence across multiple countries, conditions and treatment schedules/modalities (Figure 1). Clinician advisors experienced in a range of therapy areas and expertise in medication adherence provided input throughout the study. The study was designed in line with best practice methods,[19–22] to inform development of a conceptual model and ultimately support development of the ADAQ©, a new generic PRO measure for assessment of medication adherence.[23]
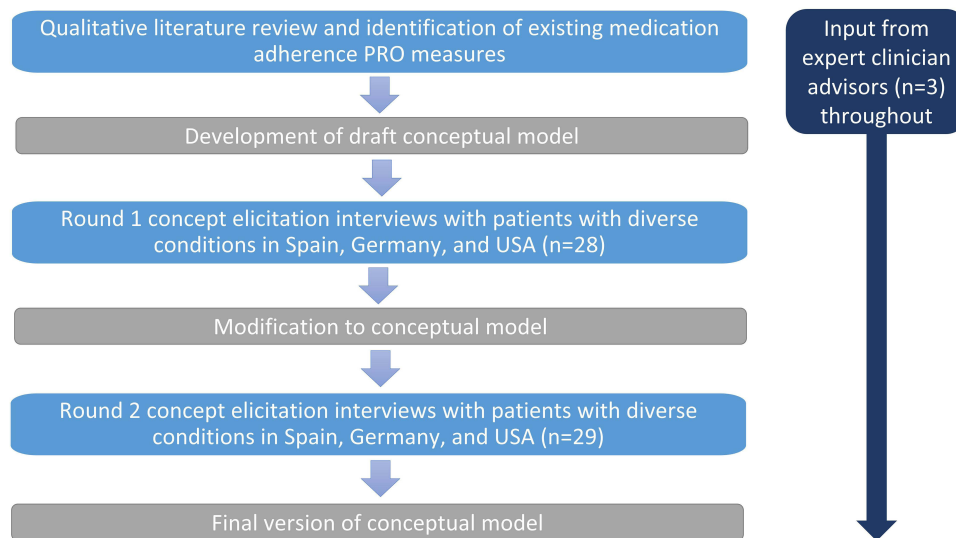
Figure 1 Study methodology.
Abbreviations: USA; United States of America, PRO; Patient-reported outcome.

Literature Review methodology

A focused literature review was conducted to identify articles reporting on qualitative research on medication adherence, or development or validation of PRO measures of medication adherence, with the aim of identifying concepts relevant to medication adherence that could be incorporated into a conceptual model. This article focuses on the qualitative medication adherence data identified. A search of bibliographic databases via the OVID SP platform was conducted, specifically within the following computerized electronic databases: PubMed (Medline); EMBASE; and PSYCHINFO. A focused search strategy, including the use of advanced keyword and subject headings (MeSH terms) and limited to the past five years (2013–2018) was implemented in Ovid SP (Appendix 1). To ensure a comprehensive evidence base, two supplementary searches were conducted: (1) the search string: "Treatment adherence" AND "patient perspective" was entered into Google Scholar and the first 20 pages of results were reviewed, and (2) once all searches were complete, a reference list review of the most pertinent articles (based on the ranking criteria described in Appendix 1) was conducted to ensure all relevant articles had been explored.

The titles and abstracts of the articles generated by the searches were exported into Excel and reviewed to identify relevant publications for full review. To be selected for review, articles were required to include at least one of the following keywords in the title and/or abstract: "adherence", "persistence", or "compliance" (specific to medication/treatment). Abstracts which met these criteria were formally ranked in terms of relevance to the topic area (see Appendix 1).

Three consecutive rounds of screening were conducted to ensure inclusion of the most relevant abstracts. In the third round of screening, conference abstracts for which full texts could not be located were removed. Due to the volume of research available, articles included for the qualitative literature review were all comprehensive literature reviews of qualitative studies from the patient perspective reporting concepts that impact or drive adherence. Full articles were assessed for relevance to the topic of interest (medication adherence), in line with the ranking criteria. All selected full-text articles were analyzed using thematic analysis principles with the help of Atlas.Ti software.[24] Thematic analysis is a method which provides a rich and detailed synthesis of qualitative data that intends to meet a specific and applied aim.[25] Results from the literature review were used to develop a preliminary conceptual model of medication adherence behaviors and helped inform the development of interview guides.

Interview Methodology

Interviews were conducted via telephone between July 2019 and March 2020 with 57 participants from the United States of America (USA; n=21), Germany (n=18), and Spain (n=18) who were receiving prescribed medications for their

condition(s) at the time of the research. The USA, Germany, and France were selected to provide representation of differing healthcare systems across American and European cultures. Participants were recruited according to pre-defined inclusion and exclusion criteria through partner recruitment agencies. Participants were adults (18+ years) who were taking prescription medication at the time of recruitment for at least one of the following conditions: asthma, hypertension, psoriasis, multiple myeloma, multiple sclerosis, diabetes, depression, and/or schizophrenia. Individuals enrolled in a clinical trial were unable to participate.

Target recruitment quotas were set to ensure a wide range of diverse chronic health conditions, treatment schedules, methods of administration (topical, oral, and injected treatments), medication types, and demographic/clinical characteristics.

Participants took part in 45-minute, one-to-one, qualitative telephone interviews. Interviews were conducted by trained qualitative interviewers. Interviews comprised a concept elicitation section (15 minutes), followed by detailed cognitive debriefing of the ADAQ© (25 minutes; reported elsewhere).[23,26] Interviews were conducted in two rounds (round 1, n=28; round 2, n=29) to allow for modifications to the conceptual model to be made following each round of interviews. Round 1 and round 2 interviews involved different groups of participants.

Semi-structured interview guides were developed based on findings from the literature review and with feedback from expert clinician advisors. The concept elicitation section of the guide ensured that all important forms and drivers of non-adherence were identified and explored. Participants were asked open-ended questions followed by more detailed probes if needed. Verbatim transcripts were qualitatively analyzed using a mix of thematic analysis and content analysis methods. ATLAS.ti software was used to highlight and group participant quotes by theme/topic.[24] The number of participants who reported a concept during the interview was calculated to provide the concept frequency. Analysis also involved exploration of concepts spontaneously versus those discussed only when probed by the interviewer. The preliminary medication adherence conceptual model developed following the literature review was updated based on the findings from the interviews.

The adequacy of the number of interviews was assessed using conceptual saturation, defined as the point at which no new concepts are reported spontaneously by participants through the conduct of further interviews.[27] Conceptual saturation was assessed by dividing the transcripts into five groups at random (in order of interview completion) and comparing the concepts that emerged spontaneously iteratively as each set of interviews was added to the dataset.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and granted an exemption from full review (due to the limited risks to participants) by a centralized review board in the USA (Western Independent Review Board). Written informed consent was obtained from all participants prior to any study activities and the collection of any data, and verbal reconfirmation of consent at the start of each interview. This informed consent included publication of anonymized participant quotes. Participants were informed of their right to withdraw from the study or to withdraw permission to use and disclose health information at any time and were paid $75/€70 to compensate them for their time to take part. All participants were given a unique identification code; their names and other identifiable information was removed from all transcripts and other documents. Prior to analysis and publication, participant data were pseudonymized.

Results

Literature Review Results

Figure 2 provides an overview of the qualitative and PRO measure review process used to select articles for data extraction, and the reasons for excluding the less relevant abstracts and articles. A total of 2168 abstracts were initially screened and after two rounds of review, 2126 abstracts were excluded. The remaining 43 full-text articles were assessed for eligibility. Four full-text articles were excluded as they contained insufficient qualitative data, were insufficiently specific, or were prospective studies. Of the 38 articles selected for data extraction, nine articles were literature reviews of qualitative research with patients about their reasons for non-adherence,[9–14,16–18] and are the focus of this manuscript.

The included articles (n=9) referred to treatment adherence among patients with 15 diseases. The most frequently mentioned disease was cancer[10,11,17] (n=3), although adherence among patients with asthma,[9,10] cystic fibrosis,[10,12] human immunodeficiency virus (HIV),[10,18] and type 2 diabetes[10,13] were each discussed in two articles. A total of 42 medication
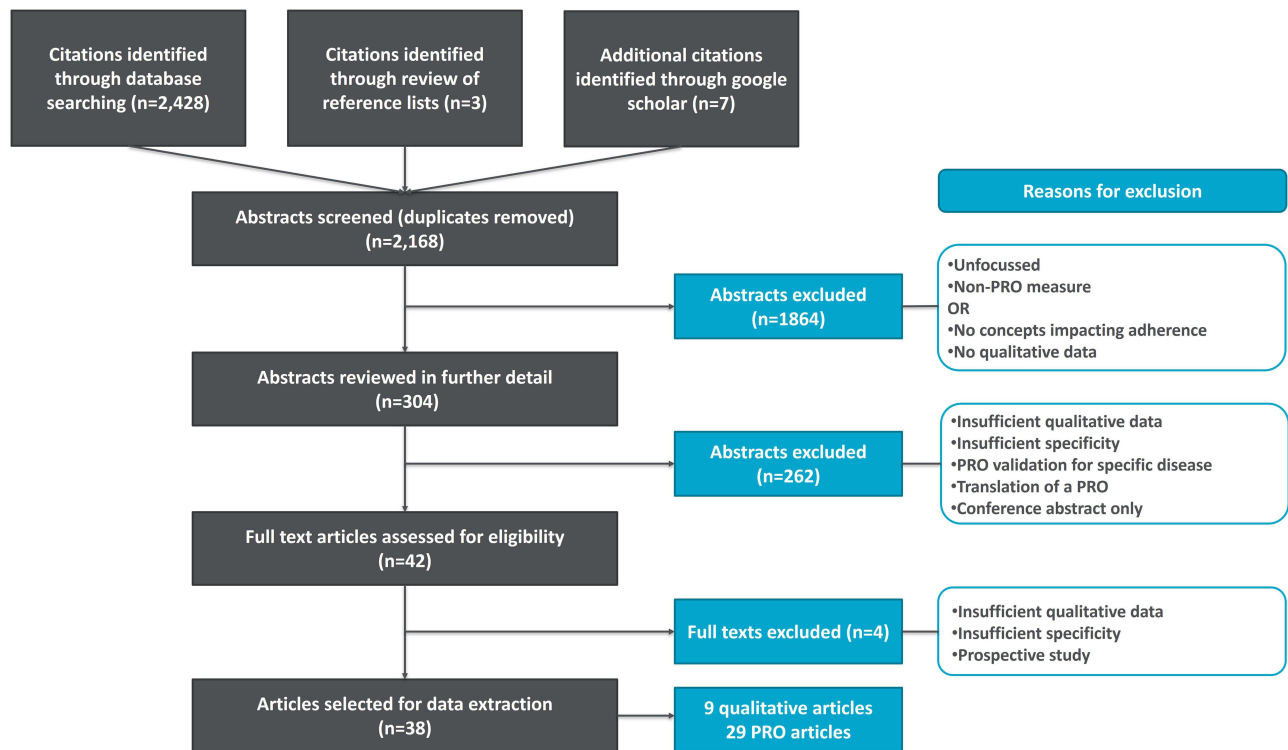
Figure 2 PRISMA-like diagram of targeted literature review search.
Abbreviations: Qual; qualitative, PRO; patient-reported outcomes.

adherence-related concepts were reported which were grouped into 10 domains; five of which were internal, patient-related concepts (beliefs and perceptions, knowledge, psychological/cognitive state, general health, routine), and five of which were primarily external to patients (societal, relationships, healthcare provision/system, treatment-related concepts, and disease).

Six concepts were referred to in almost all (n≥7) articles:

- Perceived treatment efficacy, the extent to which individuals think their treatment is working
- Involved in disease management, the extent to which there is collaboration between patients, health care professionals, and caregivers in planning and managing the disease
- Understanding of treatment, whether patients understand the purpose, mode of action, and mode of administration of their treatment
- Relationships with health care professionals, the quality of communication and interaction between patients and health care professionals
- Social support, the extent to which peers, friends, and family members encourage or discourage medication adherence
- Adverse effects, both the occurrence and fear of adverse and side-effects

Further information regarding the most commonly reported concepts are included in Appendix 2. The preliminary conceptual model developed based on the literature review is provided in Appendix 3.

Interview Results
Participant Demographic and Clinical Characteristics
Target recruitment quotas set for age, gender, race, education level, and condition were all met ensuring a diverse sample (Table 1). Participants were taking prescribed medication for a range of different conditions, with a variety of different modes of administration. Some participants were taking more than one medication for their primary condition.

Table 1 Participant Demographic and Clinical Characteristics

	R1 (n=28)	R2 (n=29)	Total (N=57)
Age, N (%)			
18 to 35 years	8 (29%)	4 (14%)	12 (21%)
36 to 60 years	16 (57%)	15 (52%)	31 (54%)
60 years plus	4 (14%)	10 (35%)	14 (25%)
Gender, N (%)			
Female	18 (64%)	14 (48%)	32 (56%)
Male	10 (36%)	15 (52%)	25 (44%)
Race, N (%)			
White/Caucasian/European heritage	19 (68%)	10 (35%)	29 (51%)
Mixed race	3 (11%)	6 (21%)	11 (16%)
White-Arabic/North African heritage	1 (4%)	8 (28%)	9 (16%)
Black/African American/African heritage	3 (11%)	5 (17%)	8 (14%)
Other (not defined)	2 (7%)	0 (0%)	2 (6%)
Education, N (%)			
Grade school	1 (4%)	1 (3%)	2 (6%)
Some high school	2 (7%)	6 (21%)	8 (14%)
High school diploma or GED	8 (29%)	13 (45%)	21 (37%)
Some years at college	10 (36%)	4 (14%)	14 (25%)
Certificate program	1 (4%)	0 (0%)	1 (2%)
University/College (2 or 4 years)	9 (32%)	3 (10%)	12 (21%)
Graduate or professional degree	0 (0%)	1 (3%)	1 (2%)
Primary condition, N (%)*			
Hypertension	5 (18%)	4 (14%)	9 (16%)
Multiple myeloma	5 (18%)	3 (10%)	8 (14%)
Asthma	5 (18%)	3 (10%)	8 (14%)
Psoriasis	4 (14%)	4 (14%)	8 (14%)
Diabetes	4 (14%)	3 (10%)	7 (12%)
Depression	4 (14%)	3 (10%)	7 (12%)
Multiple sclerosis	4 (14%)	3 (10%)	7 (12%)
Schizophrenia	3 (11%)	3 (10%)	6 (10%)
Presence of comorbidities, N (%)**			
Yes	17 (61%)	19 (66%)	36 (63%)
No	11 (39%)	10 (34%)	21 (37%)
Mode of medication administration for condition, N (%)***			
Oral pills	21 (75%)	18 (62%)	39 (68%)
Inhalation	6 (21%)	4 (14%)	10 (17%)
Injection under skin	5 (18%)	5 (17%)	10 (17%)
Applied to skin	6 (21%)	3 (10%)	9 (16%)
Injection into vein	1 (4%)	5 (17%)	6 (11%)
Oral liquids	2 (7%)	0 (0%)	2 (4%)
Infusion	0 (0%)	1 (3%)	1 (2%)
Injection (not specified)	0 (0%)	1 (3%)	1 (2%)
Total number of medications taken, N (%) One			
One	5 (18%)	6 (21%)	11 (16%)
Two to four	20 (71%)	21 (72%)	41 (72%)
Five to nine	3 (11%)	1 (3%)	4 (7%)
Ten or more	0 (0%)	1 (3%)	1 (2%)

Notes: *Several participants had multiple primary conditions. **Comorbidities included any other conditions that participants had other than the primary condition. ***Multiple options selected if more than one medication was taken for a condition.
Abbreviations: GED, General Education Development; N, number of participants; R1, round 1; R2, round 2.

Forms of Non-Adherence

Throughout the interviews, a total of eight forms of non-adherence to prescribed medications were reported (Figure 3). The most commonly reported form of non-adherence was skipping a dose (n=36/57; 63.2%). However, half of the participants also reported taking medication later than prescribed (n=29/57; 50.9%) and a quarter of participants reported taking more medication than prescribed (n=15/57; 26.3%). Illustrative quotes are provided below. Further details regarding identified concepts and additional quotes are provided in Appendix 4.

> Well, the pills are fine; I just sometimes forget the one for hypertension. I do have it in my pill box but sometimes I am a bit confused and, unfortunately, do forget to take it. It does not happen every day, but every now and then. (German participant with multiple myeloma)

> Sometimes, if I see that I've forgotten in the morning and maybe I remember at noon, I'll take it at noon. (Spanish participant with hypertension)

> Or, uh, you decided—you weren't sure if you could in the morning and you decided to take, um, more later on. And then you realize when you do—when you count the pills that there is a few missing and you realize you ended up taking them, um, uh, you know, you doubled up. (USA participant with multiple sclerosis)

Some forms of non-adherence to medication were more prevalent for participants with certain conditions and/or particular modes of administration (Figure 3). For example, larger proportions of participants with asthma and psoriasis reported skipping a dose of medication. Participants with multiple myeloma, who generally had medication administered by a health care professional, reported never taking different amounts of medication than prescribed. A limited number of participants explained that they sometimes failed to take their medication with or without food (when they should have done the opposite), that they substituted their prescribed medication for other medication, or did not clean their skin before use of the medication.

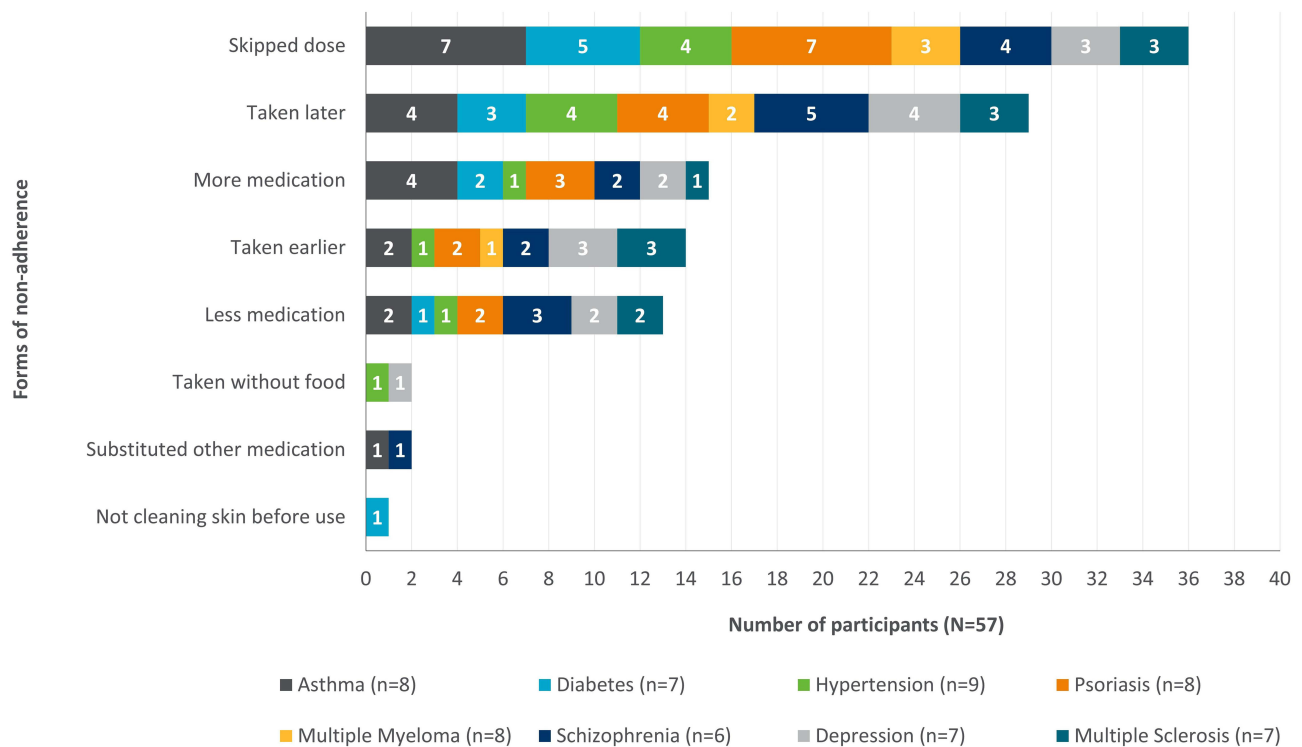> I, I don't—if I don't need it, I don't use it. (USA participant with asthma)

Figure 3 Forms of non-adherence reported by condition.

Drivers of Non-Adherence

A total of 27 drivers of medication non-adherence were reported throughout the interviews (Figure 4). The most commonly reported driver of non-adherence was forgetfulness (n=35/57; 61.4%), followed by being out of their usual routine (n=31/57; 54.4%), or being busy (n=22/57; 38.6%).

> With the tablets, there is always something that distracts me. In the mornings I tell myself I have to take the tablet but then I forget all about it because my socks bother me or because I have to shut the window (German participant with multiple myeloma)

> I mean if I'm doing something… away from home like either on vacation or somewhere else…you know, I try to work around that, but, you know, if I'm somewhere where I'm not on my regular routine, uh, it does become a little difficult sometimes to have to take. (USA participant with diabetes)

Many drivers of medication non-adherence were closely related; in particular, forgetfulness was often linked to being busy or out of their usual routine. Further, participants who commented that they did not accept the sick role (ie they did not consider that they were ill) were less likely to believe that their medication was necessary. Further, it was evident that some drivers of medication non-adherence may be more relevant to specific conditions or forms of administration. Greater proportions of participants with asthma, psoriasis, diabetes, hypertension and schizophrenia reported various forms and drivers of medication non-adherence than those with multiple myeloma and multiple sclerosis. Specifically, most drivers were reported least frequently by participants taking medication administered via intravenous injection. In
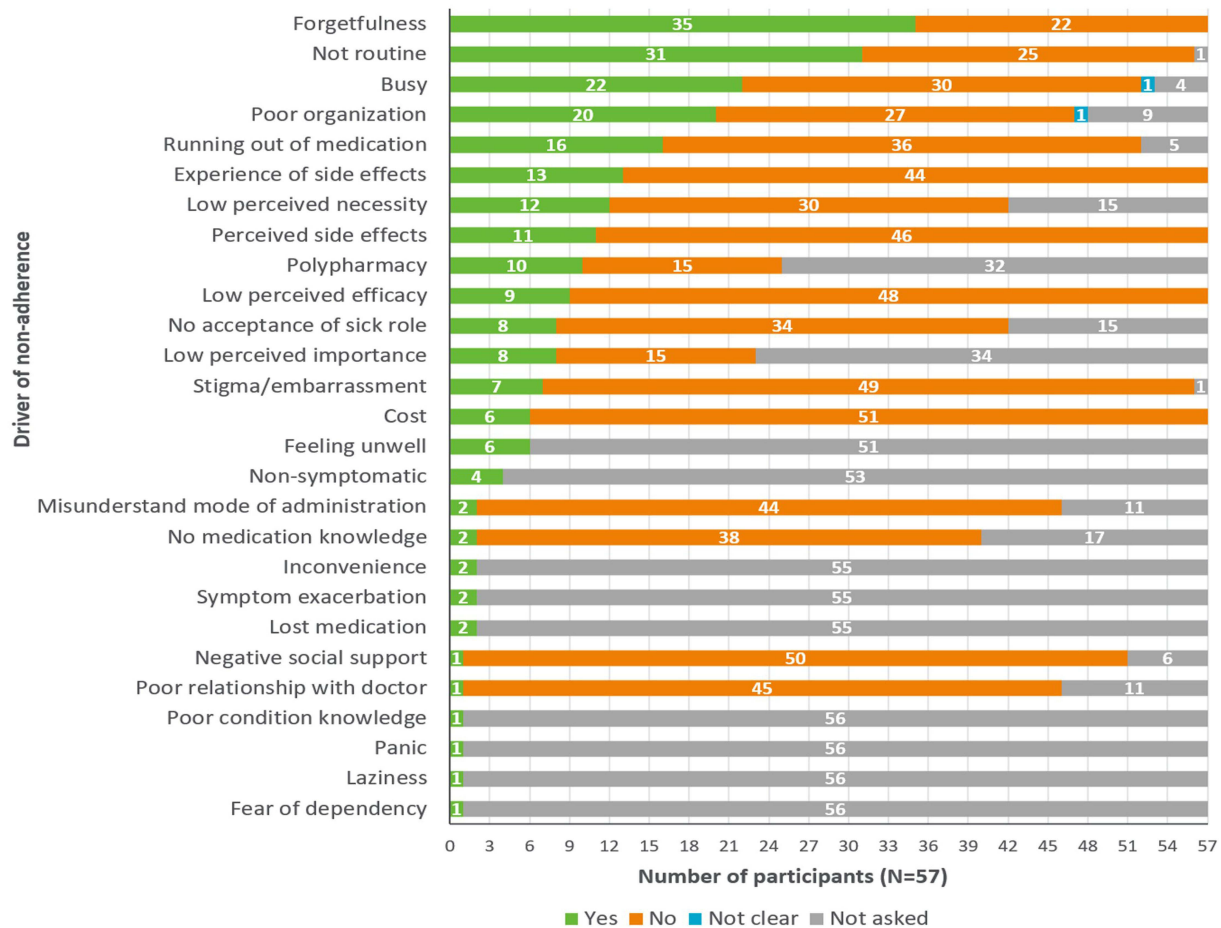

Figure 4 Drivers of non-adherence.

addition, participants with schizophrenia (n=4/6; 66.7%) were more likely to report medication non-adherence because they did not want others to see them take medication than was the case for other conditions.

> I mean, you know, I like to be more private and discrete so by me just popping a pill and taking it like that, you know, they could be thinking I'm, you know, uh, doing anything else, like doing drugs or something like that. You know, they don't know what I'm taking it for, you know. (USA participant with schizophrenia)

There was also variation in medication adherence behaviors based on demographic characteristics. More US participants reported non-adherence due to cost (n=5/21; 23.8%) and low perceived efficacy (n=6/21, 28.6%) than Spanish (cost n=1/18, 5.6%; efficacy n=2/18, 11.1%) or German (cost n=0/18; efficacy n=1/18; 5.6%) participants. Of the participants who took multiple medications, those aged ≥60 (n=5/10, 50.0%) were more likely than younger participants (n=5/28, 17.9%) to report non-adherence due to polypharmacy. Participants educated beyond high school reported higher levels of non-adherence than counterparts with only high school education or less.

Updated Conceptual Model

Findings from the qualitative interviews were used to update the preliminary conceptual model (Figure 4). While a substantive number of concepts were identified across the literature review and qualitative interviews, eight new concepts were identified through the interviews (indicated by an asterisk in Figure 5). Most prominently, these include taking medication at a different time than instructed (earlier or later), or taking a different amount of medication (more or less) than prescribed. Other concepts not identified in the literature included non-adherence due to low perceived medication necessity, and due to participants not being in their usual routine.

During saturation analysis, the following concepts were reported only in the last set of interviews and therefore did not achieve saturation: "no medication knowledge", "lost medication", and a "poor relationship with the HCP". These concepts were reported n≤2 participants each and therefore appear to be less important to medication adherence for the conditions and modes of administration included in this study. For this reason, it was concluded that no further interviews were required and that all important concepts had been identified.
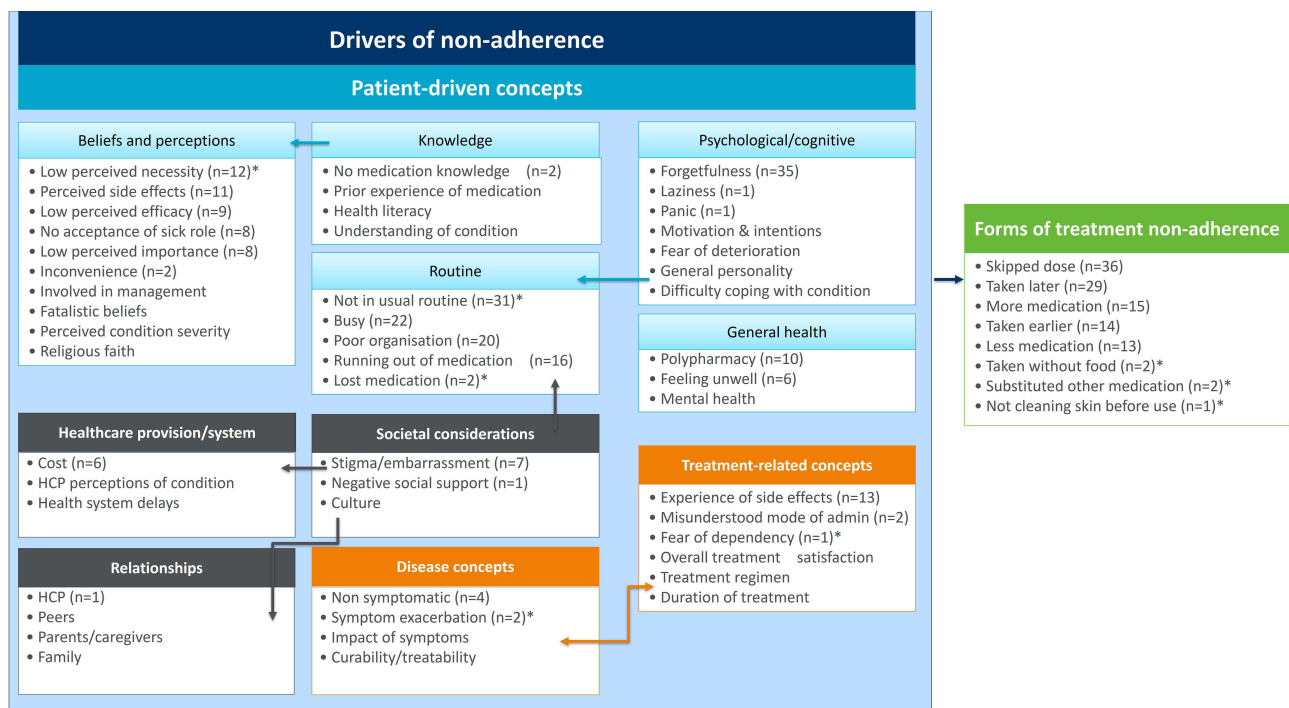

Figure 5 Medication adherence conceptual model.
Note: Number in brackets denotes the number of participants who reported the concept in the qualitative interviews. *Concepts not identified in the qualitative literature.

Discussion

This targeted review of qualitative literature and concept elicitation interviews provides an in-depth understanding of forms and drivers of medication adherence that arise across multiple conditions, modes of administration, treatment schedules, countries, ages, races, and levels of education. The breadth of concepts identified in the literature review indicate that medication adherence is influenced by a variety of behaviors and contextual factors, which determine an individual's reasons for non-adherence. These findings were supported and confirmed by the qualitative interviews. Moreover, the interviews provided more depth of understanding of the different modes of non-adherence in a diverse sample, and provided evidence of numerous drivers and forms of non-adherence. The findings from this research ultimately informed the development of a new generic PRO measure, the Adelphi Adherence Questionnaire (ADAQ©), which has been previously described and can be used in clinical practice or patient-focused research to understand barriers to adherence across conditions and treatments.[23,26]

This research supports previous findings suggesting variation in the prevalence, forms and drivers of non-adherence, based on individuals' demographic and clinical characteristics.[28,29] The identified concepts also align with those reported by the WHO.[30] However, we know of no other single study that has performed qualitative exploration of non-adherence across so many different conditions, modes of administration and countries.

Some drivers may be more closely associated with certain conditions. For example, the stigma around mental illness, and specifically schizophrenia may be the reason that participants with schizophrenia were more likely to report non-adherence due to not wanting others to see them taking medication. Additionally, individuals with conditions that involve "flares" or "episodes" of worsened symptoms (such as asthma) may be more likely to skip medication if they do not feel that they need it. Higher prevalence of non-adherence due to medication costs in the USA, as compared to Germany and Spain was unsurprising, considering the private health care system in the USA, compared to the subsidized and social welfare models in Germany and Spain.

In the present study, one of the notable findings was that participants with higher levels of education tended to report more drivers and forms of non-adherence than their less educated counterparts. The opposite relationship has been found in previous studies.[31] However, in the present study, there was overlap between participants with education above the high school level and those with asthma or hypertension. Nonadherence was also more common for those with asthma or hypertension; thus, it is unclear whether education or medical condition was driving these differences. It should also be recognized that this was a relatively small, qualitative sample in which to examine such differences – further study in larger samples is recommended.

Existing models of medication adherence, such as the Conceptual Model of Adherence to Anticoagulants developed by Brown et al,[32] the Information-Motivation-Behavioural skills model adapted by Mayberry and Osborn,[33] and the conceptual framework on factors associated with medication adherence in diabetes developed by Jaam and Kheir,[34] contain domains similar to those identified in this research. Several existing models[32,33] refer primarily to patient knowledge and motivations as factors which impact patient behavior, which in turn impacts treatment adherence. These models present a largely linear relationship between the concepts, and only briefly refer to external factors (such as healthcare systems) as having an influence on patient adherence to treatment. The simplicity of these models provides a clear image of how some patient factors impact medication adherence; however, they attribute medication adherence primarily to patient behaviors, giving insufficient attention to the role of external factors such as treatment cost, HCP relationships and disease symptoms.

More complex models exist, such as the conceptual framework on factors associated with medication adherence in diabetes developed by Jaam and Kheir,[34] which consider additional external impacts on treatment adherence, including disease characteristics, medication characteristics, dynamics with HCPs, and healthcare system-related factors. However, even these more complex models do not include information about the various forms of medication adherence. Moreover, certain forms of medication adherence were not identified in the qualitative literature reviewed. The forms of non-adherence may be particularly important when considering appropriate interventions. We suggest that the detailed, patient-focused conceptual model created here provides a holistic understanding of medication adherence.

In terms of limitations, it is possible that some of the reviewed articles may lack sufficient qualitative detail regarding medication adherence concepts. To ensure that a wide scope of qualitative evidence was identified for different therapeutic areas and given the breadth of research available in specific conditions, only literature reviews of qualitative medication adherence research were included. Several reviewed publications focused on quantitative predictors of adherence.[9–11,14,17,18] However, the breadth of concepts across different therapeutic areas was appropriate for the aims of the study. Furthermore, with regard to the qualitative interviews, most participants in the study reported being highly adherent to their medication which may have impacted

the concepts identified. This may be a product of volunteer bias. While one of the strengths of the qualitative interviews was the inclusion of a diverse sample of participants with a range of conditions, modes of administration, medication schedules, and countries, there are many other health conditions, treatment types, and countries that could not feasibly be represented. Further study in other countries and cultures (particularly in Asia, South America, and Africa) and health conditions would provide greater confidence of the relevance across populations and the generalizability of results.

Conclusion

This review of qualitative literature and concept elicitation interviews supported development of a conceptual model that provides a comprehensive summary of drivers and forms of medication adherence that can be applied across numerous conditions, modes of administrations, medication schedules, countries, ages, races, and education levels. This conceptual model can be used by clinicians to better understand and interpret barriers to medication adherence and, as such, might support decisions around interventions or support packages that could improve adherence.

Data Sharing Statement

Transcripts from the interviews are not able to be shared for data protection purposes.

Acknowledgments

Funding

Disclosure

SB, RA, VH, and JP are employees of Adelphi Group Ltd, and EE and LM were employees of Adelphi Group Ltd when the research was conducted. RR, NR, and KK were contracted by Adelphi Group Ltd to provide clinical advice throughout this project. KK reports grants from AstraZeneca, personal fees from AstraZeneca, grants from Novartis, personal fees from Novartis, personal fees from Sanofi-Aventis, grants from Sanofi-Aventis, grants from Lilly, personal fees from Lilly, grants from Merck Sharp & Dohme, personal fees from Merck Sharp & Dohme, personal fees from Boehringer Ingelheim, grants from Boehringer Ingelheim, personal fees from Bayer, personal fees from Abbott, personal fees from Amgen, personal fees from Napp, personal fees from Roche, grants from Servier, personal fees from Servier, Study Lead for UK Oramed Pharmaceuticals, Study Lead for UK Applied Therapeutics, during the conduct of the study and is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands and the NIHR Leicester Biomedical Research Centre. NR reports grants and personal fees from Boehringer Ingelheim, Novartis, Pfizer, GlaxoSmithKline and personal fees from MSD, AstraZeneca, Chiesi, Sanofi and Zambon. RR reports grants from the National Institutes of Health and the Patient-Centered Outcomes Research Institute. The authors report no other conflicts of interest in this work.

References

1. De Geest S, Sabaté E. Adherence to long-term therapies: evidence for action. *Eur J Cardiovasc Nurs*. 2003;2(4):323. doi:10.1016/S1474-5151(03)00091-4
2. Steiner JF, Earnest MA. The language of medication-taking. *Ann Internal Med*. 2000;132(11):926–930. doi:10.7326/0003-4819-132-11-200006060-00026
3. Brown MT, Bussell JK. *Medication Adherence: WHO Cares?* Elsevier; 2011:304–314.
4. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. *Oman Med Journal*. 2011;26(3):155. doi:10.5001/omj.2011.38
5. Cheen MHH, Tan YZ, Oh LF, Wee HL, Thumboo J. Prevalence of and factors associated with primary medication non-adherence in chronic disease: a systematic review and meta-analysis. *Int J Clin Pract*. 2019;73(6):e13350. doi:10.1111/ijcp.13350
6. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: systematic review and meta-analysis. *Preventive Med*. 2017;99:269–276. doi:10.1016/j.ypmed.2017.03.008
7. Khunti K, Seidu S, Kunutsor S, Davies M. Association between adherence to pharmacotherapy and outcomes in type 2 diabetes: a meta-analysis. *Diabetes Care*. 2017;40(11):1588–1596. doi:10.2337/dc16-1925
8. Fitzpatrick C, Gillies C, Seidu S, et al. Effect of pragmatic versus explanatory interventions on medication adherence in people with cardiometabolic conditions: a systematic review and meta-analysis. *BMJ Open*. 2020;10(7):e036575. doi:10.1136/bmjopen-2019-036575
9. Ahmad A, Sorensen K. Enabling and hindering factors influencing adherence to asthma treatment among adolescents: a systematic literature review. *J Asthma*. 2016;53(8):862–878. doi:10.3109/02770903.2016.1155217

10. Hanghøj S, Boisen KA. Self-reported barriers to medication adherence among chronically ill adolescents: a systematic review. *J Adolesc Health*. 2014;54(2):121–138. doi:10.1016/j.jadohealth.2013.08.009

11. Huang W-C, Chen C-Y, Lin S-J, Chang C-S. Medication adherence to oral anticancer drugs: systematic review. *Expert Rev Anticancer Ther*. 2016;16(4):423–432. doi:10.1586/14737140.2016.1159515

12. Macdonald M, Martin-Misener R, Helwig M, et al. Experiences of adults with cystic fibrosis in adhering to medication regimens: a qualitative systematic review. *JBI Datab System Rev Implement Rep*. 2016;14(5):258–285. doi:10.11124/JBISRIR-2016-002362

13. McSharry J, McGowan L, Farmer A, French D. Perceptions and experiences of taking oral medications for the treatment of Type 2 diabetes mellitus: a systematic review and meta-synthesis of qualitative studies. *Diabetic Med*. 2016;33(10):1330–1338. doi:10.1111/dme.13152

14. Rebafka A. Medication Adherence After Renal Transplantation—a Review of the Literature. *J Renal Care*. 2016;42(4):239–256. doi:10.1111/jorc.12181

15. Rezaei M, Valiee S, Tahan M, Ebtekar F, Gheshlagh RG. Barriers of medication adherence in patients with type-2 diabetes: a pilot qualitative study. *Diabetes Metabol Synd Obes*. 2019;12:589. doi:10.2147/DMSO.S197159

16. Dockerty T, Latham S, Smith T. Why don't patients take their analgesics? A meta-ethnography assessing the perceptions of medication adherence in patients with osteoarthritis. *Rheumatol Int*. 2016;36(5):731–739. doi:10.1007/s00296-016-3457-8

17. Lin C, Clark R, Tu P, Bosworth HB, Zullig LL. Breast cancer oral anti-cancer medication adherence: a systematic review of psychosocial motivators and barriers. *Breast Cancer Res Treat*. 2017;165(2):247–260. doi:10.1007/s10549-017-4317-2

18. Vitalis D. Factors affecting antiretroviral therapy adherence among HIV-positive pregnant and postpartum women: an adapted systematic review. *Int J STD AIDS*. 2013;24(6):427–432. doi:10.1177/0956462412472807

19. US Food and Drug Administration (FDA), Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims; 2009 Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.

20. US Food and Drug Administration (FDA), Patient-focused drug development: collecting comprehensive and representative input; guidance for industry, food and drug administration staff, and other stakeholders; 2020 Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input.

21. US Food and Drug Administration (FDA), Patient-focused drug development: methods to identify what is important to patients guidance for industry, food and drug administration staff, and other stakeholders; 2022 Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients.

22. Willis GB Cognitive Interviewing: A tool for improving questionnaire design (National Cancer Institute). 2004.

23. Bentley SM, Morgan L, Exall E, Arbuckle R, Rossom RC, Roche N, Khunti K, Higgins V, Piercy J. Qualitative interviews to support development and cognitive debriefing of the Adelphi Adherence Questionnaire (ADAQ©): A patient-reported measure of medication adherence developed for use in a range of diseases, treatment modalities, and countries. *Patient Prefer Adherence*. 2022;15(16):2579–2592. doi:10.2147/PPA.S358046.

24. ATLAS.ti Scientific Software Development GmbH, ATLAS.ti (version 8) [Qualitative data analysis software] https://atlas.com ; 2020.

25. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. 2006;3(2):77–101. doi:10.1191/1478088706qp063oa

26. Bentley SM, Exall L, Roberts A, Rossom R, Roche N, Khunti K, Higgins V, Arbuckle R, Piercy J. Cognitive debriefing of the Adelphi Adherence Questionnaire (ADAQ©): a novel generic patient-reported measure of medication adherence drivers and behaviours. International Society of Quality of Life Research (ISOQOL); 2021.

27. Kerr C, Nixon A, Wild D. Assessing and demonstrating data saturation in qualitative inquiry supporting patient-reported outcomes research. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10(3):269–281. doi:10.1586/erp.10.30

28. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. *Clin Med Res*. 2013;11(2):54–65. doi:10.3121/cmr.2013.1113

29. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. 2008;28(4):437–443. doi:10.1592/phco.28.4.437

30. World Health Organization. Adherence to long-term therapies. Available from: https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed September 24, 2021.

31. Golin CE, Liu H, Hays RD, et al. A prospective study of predictors of adherence to combination antiretroviral medication. *J Gen Intern Med*. 2002;17(10):756–765. doi:10.1046/j.1525-1497.2002.11214.x

32. Brown TM, Siu K, Walker D, Pladevall-Vila M, Sander S, Mordin M. Development of a conceptual model of adherence to oral anticoagulants to reduce risk of stroke in patients with atrial fibrillation. *J Managed Care Pharm*. 2012;18(5):351–362. doi:10.18553/jmcp.2012.18.5.351

33. Mayberry LS, Osborn CY. Empirical validation of the information–motivation–behavioral skills model of diabetes medication adherence: a framework for intervention. *Diabetes Care*. 2014;2:131828.

34. Jaam M, Ibrahim MM, Kheir N, Awaisu A. A proposed holistic conceptual framework for barriers to medication adherence in diabetes. *Value Health*. 2016;19(7):A676–A677. doi:10.1016/j.jval.2016.09.1897