

**A framework for understanding sources of bias in medication adherence research**

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1 **A framework for understanding sources of bias in medication adherence**
2 **research**

3

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19

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27 **Abstract**

28 The sources of bias in medication adherence research have not been comprehensively explored.
29 We aimed to identify biases expected to affect adherence research and to develop a framework
30 for mapping these onto the phases of adherence (initiation, implementation, and
31 discontinuation). A literature search was conducted, key papers were reviewed and a Catalogue
32 of Bias was consulted. The specific biases related to adherence measurement and metrics were
33 mapped onto the phases of adherence using a tabular matrix. Twenty-three biases were
34 identified, of which 11 were specifically relevant to adherence measures and metrics. The
35 mapping framework showed differences in the numbers and types of biases associated with
36 each measure and metric while highlighting those common to many adherence study designs
37 (e.g. unacceptability bias, apprehension bias). The framework will inform the design of
38 adherence studies and the development of risk of bias tools for adherence research.

39

40 **What is already known about this subject**

- 41 • Medication adherence information in published papers is highly variable in quality,
42 consistency in reporting and reproducibility.
- 43 • A comprehensive understanding of the methodological challenges in adherence
44 research, including the sources and risks of bias, is needed to improve study design,
45 data analysis and reporting.

46 **What this study adds**

- 47 • We have identified and defined 23 sources of bias expected to affect the design and
48 interpretation of research intended to collect adherence information.
- 49 • We have developed a framework for mapping biases relevant to measuring and
50 reporting adherence information onto each phase of adherence.
- 51 • The mapping matrix is intended to inform the design of future adherence studies and to
52 facilitate the development of tools to identify biases and mitigate their effects in
53 medication adherence research.

54

55 **Introduction**

56 Suboptimal medication adherence has long been recognised as a major determinant of poor
57 treatment response [1]. Research in this area has been growing steadily in the past 50 years,
58 thanks in part to the seminal work lead by Haynes, Taylor and Sackett [2, 3]. Two conferences
59 were convened in the 1970's resulting in calls for more research to understand the magnitude
60 and determinants of suboptimal adherence, the best measurement methods, and strategies for
61 helping patients to take their medications in clinical practice. While these agendas remain
62 prominent, an increasing amount of work is needed to understand the methodological
63 challenges posed by adherence research and to create a more reliable and accurate evidence
64 base for adherence information [1, 4-7]. This is driven, in part, by growing concerns about the
65 quality and reproducibility of the outputs of adherence research, particularly regarding the
66 measurement of adherence across different healthcare contexts (e.g. patient care, clinical trials,
67 adherence service provision). The Ascertaining Barriers for Compliance (ABC) taxonomy [8],
68 the Timelines-Events-Objectives-Sources (TEOS) framework [5, 6], the ESPACOMP
69 Medication Adherence Reporting Guideline (EMERGE) [4], and other works have highlighted
70 that measurement methods and the different phases of adherence (initiation, implementation,
71 and discontinuation) are interlinked and must be considered carefully when planning adherence
72 studies.

73 Concerns relating to biases in the design and interpretation of adherence studies have been
74 raised [9, 10]. In particular, the biases encountered using different measurement methods to
75 quantify adherence (e.g. pill counts, analysis of refill databases) and different metrics to
76 summarise individual adherence behaviour (e.g. percent of doses taken, Proportion of Days
77 Covered (PDC) [11]) have not been extensively examined. In addition, it is unclear how the
78 biases might differ depending on the adherence phase being studied. Therefore, the aims of this
79 research were to:

- 80 (1) identify sources of bias expected to affect the design and interpretation of studies
81 intended to collect adherence information;
- 82 (2) develop a framework for mapping biases onto the phases of adherence and the
83 measurement methods and metrics commonly used in adherence research.

84 **Methods**

85 *Identifying sources of bias in adherence research*

86 We conducted a literature search to identify and collate sources of bias expected to affect
87 adherence research. While the general principles of literature searching outlined in the
88 PRISMA guidelines [12] were adhered to in some components of the search, this was a rapid
89 review [13], and not intended to be systematic.

90 The literature search was conducted using Ovid MEDLINE, Ovid Embase, Scopus, and Web
91 of Science. The search was conducted from the start date of the respective databases to January
92 2023. Advanced search strategies were used for all searches. The following database-specific
93 vocabulary (e.g. Medical Subject Headings) and keywords were combined with Boolean

94 operators to identify relevant literature; ‘bias*’, ‘limitation*’, ‘medication adherence’,
95 ‘adherence research’, ‘adherence study design’, ‘adherence measure*’, ‘adherence metric*’,
96 ‘measurement method*’, ‘measuring medication adherence’. Respective database-specific
97 vocabulary items were used, where permitted, in the following databases: Ovid MEDLINE,
98 and Ovid Embase. Details of the search strategy are presented in Table A1.

99 Papers were included if they contained information or discussions about sources of biases
100 and/or limitations in adherence research. The search was not limited by year or language of
101 publication or by article type.

102 Papers were screened based on the study title and abstract. Any duplicate records were
103 removed. Papers retained after screening were reviewed for inclusion criteria based on the full
104 text. All searches, paper screening, and full text assessments were conducted by KS and
105 subsequently checked by DW. Sources of bias discussed in the papers were identified and
106 extracted.

107 Key review papers and ESPACOMP-endorsed outputs were mined for additional papers (e.g.
108 the EMERGE guidelines [4] and the TEOS framework [5]). The Oxford Catalogue of Bias [14]
109 was consulted and relevant biases were identified and summarised.

110 In all cases, the criteria for deciding if the sources of bias were relevant to adherence research
111 were; 1) the bias could be clearly linked to aspects of adherence study design, study conduct
112 or reporting, 2) author consensus, and 3) consultation with experts in the working group of the
113 Centre for Business Innovation Medical Adherence and Digital Health consortium.

114 The following data were extracted from included studies:

- 115 1. First author and year of publication.
- 116 2. Paper title and design (e.g. randomized controlled trials, systematic reviews,
117 commentaries).
- 118 3. The aim(s) or primary purpose of the work.
- 119 4. The type of adherence study conducted or discussed, as defined by Wright et al. [1] i.e.:
120 1) studies that explore the causes of suboptimal adherence; 2) studies designed to
121 understand the consequences of suboptimal adherence; 3) studies that propose
122 mitigation strategies to improve adherence; and 4) studies aimed to strengthen the
123 methodological aspects of adherence research.
- 124 5. Findings related to study bias and/or limitations.
- 125 6. Specific types of biases identified and/or discussed.

126 *Framework development*

127 The framework was developed based on the assumption that biases in adherence research need
128 to be understood in the context of three key factors:

- 129 1. The methods used to quantify adherence. Here we distinguish adherence ‘measures’,
130 i.e. the methods used to collect adherence information, from adherence ‘metrics’ – the

131 quantitative data items that capture the adherence behaviour for each person. We
132 considered these separately.

- 133 2. The phases of adherence, as defined by the ESPACOMP-endorsed ABC taxonomy:
134 initiation (when the individual takes the first dose of the prescribed medication),
135 implementation (the extent to which the individual's actual dosing corresponds to the
136 prescribed dosing regimen), and discontinuation (when the individual takes no more
137 doses, thereby marking the end of therapy) [8].
- 138 3. We therefore propose that adherence research can be understood to have four
139 components (Figure A1): 1) the phase of adherence under investigation; 2) the method
140 used to measure adherence; 3) the metric used to quantify the adherence behaviour for
141 each individual; and 4) the summary adherence outcome reported across participants.

142 We mapped the sources of bias onto the phases of adherence and the measures and metrics
143 used in the study methods using a tabular matrix. Of the biases identified to be important for
144 adherence research, only those related specifically to adherence measures and metrics were
145 included in the mapping. Biases related to aspects of general study design not specific to
146 adherence measures and metrics, e.g. randomization, blinding, and confounding, were not
147 included.

148 The adherence measures considered included (but were not limited to): 1)
149 self/caregiver/healthcare-provider reports, questionnaires, diaries, or interviews; 2) pill counts
150 at specific points in time (e.g. at prescription or study medication refill); 3) analysis of
151 prescription or claims databases; 4) analysis of electronically monitored therapy (e.g. MEMS
152 [15]); 5) observed therapy—any method in which the study subject is observed taking the
153 medication; and 6) any method in which adherence is monitored using drug plasma
154 concentrations or biomarkers.

155 The adherence metrics for individual study participants included (but were not limited to): 1)
156 questionnaire or interview scores; 2) the quantity of medication taken compared with the
157 prescribed quantity over a specified time (usually expressed as a percent); 3) medication
158 possession or availability scores (e.g. the Proportion of Days Covered (PDC) [11] or
159 Medication Possession Ratio (MPR) [11]); 4) medication-taking events summaries for
160 electronically monitored therapy; 5) parameters relating to plasma concentrations or
161 biomarkers.

162 **Results**

163 We identified 389 relevant publications. We removed duplicates and screened 156 reports by
164 titles and abstracts; 80 reports qualified for full text assessment, of which 42 met the eligibility
165 criteria. No papers required translation into English. A flow diagram for the literature selection
166 is provided in Figure A2.

167 A summary of the included reports and the biases extracted from each is presented in Table
168 A2. Of the 42 reports, 17 were systematic reviews examining the effects of clinical
169 interventions on adherence [10, 16-31]. These reports included a risk of bias assessment using

170 either the Cochrane Risk of Bias tool [32] or the Newcastle–Ottawa tool [22]. One report
171 assessed the methodological quality of the included studies using the Joanna Briggs quality
172 checklist [33]. Twenty reports focused on methodological aspects of adherence research,
173 including: 1) operational definitions of adherence [5]; 2) optimal thresholds for measuring
174 adherence in large databases [33]; 3) comparisons of adherence measures [34]; 4) correlation
175 between objective and patient-reported adherence measures [35-37]; and 5) validation of
176 measurement instruments (e.g. visual analogue scales) for adherence behaviour [38]. Ten of
177 the 20 papers [39-48] reported key advantages and limitations for different adherence
178 measures, which are summarised in Table A3. The remaining papers included three review
179 papers assessing the magnitude of suboptimal adherence in particular patient groups [49-51]
180 and two commentaries [52, 53].

181 In total, we identified 16 major sources of bias from the published papers (no identified biases
182 were excluded), along with a further seven biases from the Oxford Catalogue of Bias; a total
183 of 23. A summary of the biases, their definitions, proposed mitigation strategies and any linked
184 biases are provided in Table 1. The definitions are based on a previously published definition
185 of “bias”: a systematic distortion, due to a design problem, an interfering factor, or a judgement,
186 that can affect the conception, design, or conduct of a study, or the collection, analysis,
187 interpretation, presentation, or discussion of outcome data, causing erroneous overestimation
188 or underestimation of the probable size of an effect or association [54].

189 The biases identified cover different aspects of adherence research. For example, attrition bias,
190 detection bias, confounding bias, and performance bias, are more relevant to the design of
191 adherence studies and implementation of study procedures. Other biases, such as reporting bias,
192 publication bias, and language bias, are more applicable to data analysis and interpretation of
193 findings from adherence studies.

194 Eleven of the 23 biases were specifically relevant to the phases of adherence, as well as
195 measures and metrics used in adherence research. These 11 biases were therefore included in
196 the development of the bias mapping framework. The tabular matrices for adherence measures
197 and metrics are presented in Table 2 and Table 3.

198 **Discussion**

199 We have identified and collated sources of bias expected to affect the design and interpretation
200 of research intended to collect adherence information. In all, 23 biases are likely to affect the
201 determination of adherence at different phases (initiation, implementation, and
202 discontinuation). We mapped 11 biases critical to the measurement of adherence across the
203 three phases, to provide a framework for understanding the major sources of biases.

204 We have combined biases discussed in the published literature and those described in the
205 Oxford Catalogue of Bias, creating a comprehensive list of biases and definitions in the context
206 of adherence research. The bias mapping frameworks provide the basis for the development of
207 a risk of bias tool, specific to adherence research. Such a tool would enable robust assessment
208 of biases when systemically reviewing published adherence studies, something not possible
209 with the currently available tools which are designed for other types of clinical research [10].

210 In addition, the mapping of relevant biases to commonly used measures and metrics can be
211 used by researchers to inform the design of future adherence studies.

212 The bias frameworks in Tables 2 and 3 show differences in the numbers and types of biases
213 associated with each measure and metric. For example, subjective measures such as
214 self/caregiver/healthcare-provider reports, questionnaires, diaries, and interviews are
215 associated with more biases than objective measures such as observed therapy or the
216 measurement of drug plasma concentrations. The Hawthorne effect and upward bias appear to
217 be more important in research that focuses on the implementation phase of adherence. It is also
218 evident that some biases will be important across several measurement methods and adherence
219 study designs.

220 The presence of bias in adherence-related research will have implications on the estimates of
221 adherence obtained which may lead to misleading study interpretations. For example, the
222 presence of ‘insensitive measure bias’ (i.e. the adherence measurement method was not suitable
223 for the data available) in a study focused on adherence service provision for any study design
224 (i.e. randomised/controlled or observational) may suggest that the service/intervention
225 effectively improved the participant’s adherence when this may not actually be the case. This
226 would similarly apply to phase 3 clinical trials where an inaccurate assessment of adherence
227 (e.g. poorly conducted pill counts) would impact the assessment of the treatment efficacy and
228 safety.

229 This work should be viewed considering some limitations. The systematic identification of
230 biases relied heavily on existing risk of bias assessment tools or published opinions about the
231 limitations of adherence measurement methods. Therefore, our current understanding of
232 sources of biases in adherence research is limited to the bias domains assessed in the existing
233 risk of bias tools. Research is currently underway in our group to develop a purpose-built risk
234 of bias tool for adherence research which will help address this. The mapping frameworks
235 focus exclusively on study bias and do not consider the additional advantages of each
236 adherence measure and metric when designing a study to align with the different phases of
237 adherence.

238 We have identified and collated biases relevant to adherence research and have developed a
239 framework for mapping biases onto the adherence phases and commonly used measures and
240 metrics. The framework for biases is intended to inform the design of adherence studies and to
241 facilitate development of tools to identify biases and mitigate their effects in medication
242 adherence research.

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245 Digital Health consortium convened by Dr Jeremy Holland for assistance with the biases
246 relevant to adherence research from the Oxford Catalogue of Bias.

247

248 **Conflicts of interest/disclosure**

249 JKA is a co-author of material published in the Oxford Catalogue of Bias. BV is a
250 shareholder and employee of AARDEX group. The other author(s) declare that they have no
251 conflicts of interest.

252

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256

257 **Data availability statement**

258 Data sharing is not applicable to this article as no new data were created or analyzed in this
259 study.

260

261 **Ethics statement**

262 Ethics approval was not required for this study.

263

264 **Author contribution**

265 KAS, DAH and DFBW conceived and designed the research; KAS, DAH and DFBW
266 conceived and produced the bias mapping table, KAS conducted the literature search; DAH,
267 SLS, DFBW reviewed the initial findings; KAS wrote the first draft of the manuscript; BV
268 and JKA reviewed the Oxford Catalogue of Bias and summarized the relevant entries; JKA
269 also framed the definitions included in Table 1; KAS, DAH, SLS, BV, JKA and DFBW
270 developed the final manuscript. All authors approved the final version.

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418 [proposed-definition](https://catalogofbias.org/2018/06/15/a-word-about-evidence-6-bias-a-proposed-definition).

419 Table 1. Types of biases expected to affect adherence research

Identified biases	Source(s)	Definition in the context of adherence research	Proposed mitigation strategies	Linked biases
Adherence bias	Oxford Catalogue of Bias	A systematic distortion in outcome data that arises when participants who adhere to a study protocol or intervention differ from those who do not adhere, when that difference relates to the outcome of interest.	Carry out intention to treat analysis and where possible, exploratory secondary analyses looking at the impact of non-adherence on the outcome of interest [14].	Attrition bias Selection bias
Apprehension bias or social desirability bias	Literature search [22, 28, 35, 38-41, 43, 45-49, 52] Oxford Catalogue of Bias	A systematic distortion in outcome data, due to altered physiological responses in an individual from those usually expected in that individual, arising from the individual's unconscious reactions to being studied.	Including methods to try and reduce the anxiety of study participants [14] such as providing supportive, reassuring and non-judgmental statements regarding medication adherence behaviour.	Hawthorne effect Upward bias or ceiling effect Insensitive measure bias
Attrition bias	Literature search [16, 20, 25, 27, 29-31] Oxford Catalogue of Bias	A systematic distortion in outcome data that arises when there is unequal loss of participants from study groups in a trial, resulting in differences between participants who continue in an adherence study and those who drop out.	Ensuring effective channels of communication between study staff and participants and allowing incentives for participants to continue in the study [14].	Compliance bias Selection bias
Availability bias	Oxford Catalogue of Bias	A systematic distortion that arises from the use of information that is most readily available, rather than that which is necessarily most representative of the true adherence data.	Consideration of the adherence information and data informing any given decision and whether this is sufficient [14].	Unacceptability bias
Confounding bias	Literature search [24] Oxford Catalogue of Bias	A systematic distortion that enhances or masks an association between two measures of adherence, because a separate factor is independently associated with each of the measures.	Methods to reduce the risk of confounding include randomisation, stratification, statistical adjustments or having a very large effect size [14].	Selection bias
Detection bias	Literature search [16, 20, 27, 29-31] Oxford Catalogue of Bias	A distortion that arises from systematic differences between groups in how an adherence intervention is delivered or an outcome assessed between study participant groups.	Ensuring adequate training amongst study staff and following well-designed protocols to ensure consistent delivery of intervention and outcome assessment.	Interviewer bias or observer bias Performance bias
Hawthorne effect	Literature search [38-40, 43] Oxford Catalogue of Bias	A change in an individual's behaviour that arises from the knowledge of being watched, resulting in altered adherence.	Using hidden observation in the study design [14].	Apprehension or social desirability bias Upward bias or ceiling effect
Healthy user bias or healthy adherer effect	Literature search [21]	A systematic distortion in adherence behaviour that occurs in patients who are more in control and engaged with their health, who are likely to be more adherent to medications than others.	Broadening the recruitment/inclusion criteria to ensure inclusion of participants that are more representative of the general population.	Selection bias Volunteer bias

Identified biases	Source(s)	Definition in the context of adherence research	Proposed mitigation strategies	Linked biases
Information bias	Literature search [46] Oxford Catalogue of Bias	A distortion that arises from systematic differences in the collection or handling of adherence information obtained in a study.	Following well-designed protocols and ensuring adequate training amongst study staff.	Insensitive measure bias Reporting bias
Insensitive measure bias	Oxford Catalogue of Bias	A systematic distortion that arises from using insufficiently accurate methods to detect the true medication adherence behaviour.	Triangulating measurement methods to increase accuracy of adherence behaviour assessed.	Apprehension or social desirability bias Information bias Interviewer bias or observer bias
Interviewer bias or observer bias	Literature search [46] Oxford Catalogue of Bias	A distortion that arises when the process of eliciting, observing, or recording information results in systematic discrepancies between the elicited, observed, or recorded adherence information and the true adherence behaviour.	Adequate training for study observers in recording adherence behaviour with clear protocols of methods and tools for collecting adherence data [14].	Detection bias Insensitive measure bias
Language bias	Literature search [28] Oxford Catalogue of Bias	A systematic distortion that arises from publication or review of adherence studies in a selected language or languages, omitting other languages.	Literature reviews should not exclude adherence studies published in languages other than their own.	No linked biases
Non-response bias	Literature search [42] Oxford Catalogue of Bias	A systematic distortion that occurs when non-responders to adherence surveys or questionnaires differ from responders (or early responders) to a sufficient extent to produce different outcomes.	Keeping adherence surveys or questionnaires succinct as possible and providing incentives for participation.	Selection bias
Novelty bias	Oxford Catalogue of Bias	A systematic distortion that arises when an adherence intervention or measurement tool appears to be better because it is new or perceived to be.	Explicitly mention in the published study if the observed difference is likely due to novelty bias [14].	No linked biases
Performance bias	Literature search [16, 20, 27, 29-31] Oxford Catalogue of Bias	A systematic distortion that arises from differences in the care and handling of study participants, owing to knowledge of allocation groups by either the researcher or the participant.	Blinding of participants and staff to the intervention however if this is not feasible, using objective outcomes instead of subjective ones may mitigate this effect [14].	Detection bias
Publication bias	Literature search [10, 16-19, 26, 29, 49, 50] Oxford Catalogue of Bias	A systematic distortion in the analysis of published data that arises when the likelihood that an adherence study will be published or not is affected by the observed outcomes of the study.	Include adherence studies not only from databases but also from trial registries or conference proceedings. Using statistical methods such as funnel plots can also help estimate if the review is impacted by this bias [14].	Reporting bias
Recall bias or memory bias	Literature search [39-43, 45, 46]	A systematic distortion that arises when there are differences in the accuracy or completeness of recall to memory of past adherence events or experiences.	Use of daily diaries to help recall adherence events rather than a summary recall.	Reporting bias Upward bias or ceiling effect

Identified biases	Source(s)	Definition in the context of adherence research	Proposed mitigation strategies	Linked biases
	Oxford Catalogue of Bias			
Reporting bias	Literature search [10, 16, 20, 27, 29-31, 36, 39, 48] Oxford Catalogue of Bias	A systematic distortion that arises from inadequate transparency or consistency in the way that adherence information is reported in a study.	Use of reporting guidelines such as the ESPACOMP Medication Adherence Reporting Guideline (EMERGE).	Information bias Publication bias
Selection bias	Literature search [16, 17, 20, 27, 29-31, 37, 39, 52] Oxford Catalogue of Bias	A distortion that arises when the procedures used to select individuals or groups into a study or into the set of data for analysis, result in systematic differences between populations, resulting in differences in adherence or apparent adherence.	Broadening the recruitment/inclusion criteria to ensure inclusion of participants that are more representative of the general population.	Attrition bias Confounding bias Compliance bias Healthy user bias or healthy adherer effect Non-response bias Starting time bias Volunteer bias
Starting time bias	Oxford Catalogue of Bias	A systematic distortion that arises when there is a failure to identify a common starting time for an exposure or a disease between different groups of participants in a study.	Include analyses to account for any differences in exposure times between participant groups.	Selection bias
Unacceptability bias	Oxford Catalogue of Bias	A distortion that arises from a systematic difference in response rates or uptake of adherence measurements, because they are unacceptable, for example if they are perceived to be potentially hurtful or embarrassing.	Ensuring participants are well informed of the study protocol prior to participating may help reduce differences in response rates.	Availability bias
Upward bias or ceiling effect^a	Literature search [33, 34, 36, 39-41, 47]	A distortion in outcome data that arises from a tendency of adherence measurements to be positively skewed.	Normalising the difficulty of remembering to take medications as well as providing supportive, reassuring and non-judgmental statements regarding medication adherence behaviour.	Apprehension bias or social desirability bias Hawthorne effect Recall bias
Volunteer bias	Oxford Catalogue of Bias	A systematic distortion that arises when participants who volunteer to take part in a study have characteristics that are different from those of the general population.	Including recruitment/inclusion criteria that would enable inclusion of participants that are more representative of the general population.	Healthy user bias or healthy adherer effect Selection bias

420 ^aDownward bias (a distortion in outcome data that arises from a tendency of adherence measurements to be negatively skewed) may correspond to upward bias.

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422 Table 2. Biases mapped to common adherence measures and the phases of adherence (initiation, implementation, and discontinuation)

	Self/caregiver/healthcare-provider reports, questionnaires, diaries, or interviews	Pill counts	Prescription and claims databases	Electronically monitored therapy	Observed therapy	Monitoring drug concentrations or biomarkers
Initiation	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Availability bias • Information bias • Insensitive measure bias • Interviewer or observer bias • Non-response bias • Recall or memory bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Availability bias • Insensitive measure bias • Unacceptability bias 	<ul style="list-style-type: none"> • Availability bias • Information bias • Insensitive measure bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Selection bias • Unacceptability bias 	<ul style="list-style-type: none"> • Unacceptability bias 	<ul style="list-style-type: none"> • Insensitive measure bias • Unacceptability bias
Implementation	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Availability bias • Hawthorne effect • Information bias • Insensitive measure bias • Interviewer or observer bias • Non-response bias • Recall or memory bias • Unacceptability bias • Upward bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Availability bias • Insensitive measure bias • Unacceptability bias • Upward bias 	<ul style="list-style-type: none"> • Availability bias • Information bias • Insensitive measure bias • Upward bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Hawthorne effect • Selection bias • Unacceptability bias 	<ul style="list-style-type: none"> • Hawthorne effect • Unacceptability bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Insensitive measure bias • Unacceptability bias
Discontinuation	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Availability bias • Information bias • Insensitive measure bias • Interviewer or observer bias • Non-response bias • Recall or memory bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Availability bias • Insensitive measure bias • Unacceptability bias 	<ul style="list-style-type: none"> • Availability bias • Information bias • Insensitive measure bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Selection bias • Unacceptability bias 	<ul style="list-style-type: none"> • Unacceptability bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Insensitive measure bias • Unacceptability bias

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425 Table 3. Biases mapped to common adherence metrics and the phases of adherence (initiation, implementation, and discontinuation)

	Questionnaire or interview scores	Percent of doses taken	Medication possession or availability scores (PDC or MPR)	Medication-taking events summary	Observed medication-taking records	Plasma concentrations or biomarkers
Initiation	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Information bias • Insensitive measure bias • Interviewer or observer bias • Non-response bias • Recall or memory bias 	<ul style="list-style-type: none"> • Insensitive measure bias 	<ul style="list-style-type: none"> • Information bias • Insensitive measure bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Information bias 	<ul style="list-style-type: none"> • Information bias 	<ul style="list-style-type: none"> • Insensitive measure bias
Implementation	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Information bias • Insensitive measure bias • Interviewer or observer bias • Non-response bias • Recall or memory bias • Upward bias 	<ul style="list-style-type: none"> • Insensitive measure bias • Upward bias 	<ul style="list-style-type: none"> • Information bias • Insensitive measure bias • Upward bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Hawthorne effect • Information bias 	<ul style="list-style-type: none"> • Information bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Insensitive measure bias
Discontinuation	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Information bias • Insensitive measure bias • Interviewer or observer bias • Non-response bias • Recall or memory bias 	<ul style="list-style-type: none"> • Insensitive measure bias 	<ul style="list-style-type: none"> • Information bias • Insensitive measure bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Information bias 	<ul style="list-style-type: none"> • Information bias 	<ul style="list-style-type: none"> • Apprehension or social desirability bias • Insensitive measure bias

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