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1 # ESPACOMP Medication Adherence Reporting Guideline (EMERGE)
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34 **ABSTRACT**

35 Medication adherence-related research applies observational, interventional and/or implementation

36 science approaches spanning multiple disciplines to assess or manage medication adherence. This

37 demands coherent conceptualization, valid methods, appropriate analyses, and complete, accurate

38 reporting. To ensure reliable reporting, the European Society for Patient Adherence, Compliance and

39 Persistence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE) recommends

40 standard reporting approaches based on an accepted taxonomy.

41 This guideline results from a literature review, a reactive e-Delphi study with 26 international

42 multidisciplinary medication adherence experts, and feedback from the ESPACOMP membership. It

43 is designed to supplement existing guidelines for health research reporting, and structured around 4

44 minimum reporting criteria and 17 items reflecting best reporting practice. By enhancing and

45 harmonizing research reporting, EMERGE aims to advance research and, ultimately, patient

46 outcomes.

47   **CHALLENGES AND SHORTCOMINGS IN MEDICATION ADHERENCE REPORTING**

48   Medication non-adherence is a major public health problem(1, 2) with significant health and

49   economic consequences.(1-4) For many conditions, taking medications as prescribed is crucial to

50   achieve optimal outcomes.(5-7) Despite more than 50 years of research, the evidence base for

51   effective interventions that can be implemented in routine clinical care remains limited.(8, 9)

52   Medication adherence-related research applies observational, interventional and/or implementation

53   science approaches across disciplines including, but not limited to medicine, pharmacy, nursing,

54   behavioral science, sociology, pharmacometrics, biostatistics and health economics.(10)

55   Unfortunately, inadequate research reporting often hampers interpretation of findings, complicates

56   data abstraction for meta-analyses and prevents study replication. Common problems of reporting

57   include unclear, inconsistent definitions;(11-14) inadequate measurement of adherence

58   outcomes;(7, 14, 15) suboptimal methods of analysis;(11-14) insufficiently detailed descriptions of

59   intervention delivery settings;(15) and scant theoretical underpinnings.(16)

60   Previous efforts to improve adherence research reporting standards(11, 17-20), have resulted in

61   guidelines and recommendations that overlap with existing health research reporting guidelines,

62   e.g., CONsolidated Standards of Reporting Trials (CONSORT),(21) STrengthening the Reporting of

63   OBservational studies in Epidemiology (STROBE),(22) Standards for Reporting Implementation

64   Studies (StaRI) Statement (StaRI).(23) These recommendations only indirectly pertain to medication

65   adherence research,(17, 19) include no clear conceptualization of medication adherence(11, 17, 19,

66   20) and focus on research methods rather than reporting.(11, 19, 20)

67   Weighing these shortcomings against evidence that guidelines endorsed by professional societies

68   and journals enhance overall health research reporting,(24-28) the European Society for Patient

69   Adherence, COMpliance, and Persistence (ESPACOMP, www.espacomp.eu, accessed: April 30th,

70   2018) developed the ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Grounded in

71   the conceptualization of medication adherence provided by the previously-reported taxonomy,(10)

72   EMERGE aims to complement existing health research reporting guidelines, increasing the

73   transparency and consistency of reporting by guiding researchers through processes specifically

74   relevant to medication adherence, as well as to those for which it is a variable of interest.

75   **Taxonomy for medication adherence**

76   EMERGE adopts the previously-reported taxonomy(10) which defines medication adherence as "the

77   process by which patients take their medications as prescribed," consisting of three interrelated yet

78   distinct phases: (A) **initiation**; (B) **implementation;** and (C) **persistence (figure 1).** Non-adherence to

79   medications can occur in any of these phases, e.g., late, incomplete, or non-initiation of the

80   prescribed treatment, sub-optimal implementation of the dosing regimen (e.g., late, skipped, extra

81   or reduced doses, drug holidays) or early discontinuation (non-persistence). Each phase poses

82   different methodological challenges related to how medication use is operationally defined,

83   measured, and analyzed.

84   **DEVELOPMENT OF EMERGE**

85   EMERGE was developed in accordance with recommendations for health research reporting

86   guideline developers(29) of the Enhancing the QUAlity and Transparency Of health Research

87   (EQUATOR) network (www.equator-network.org, accessed: April 30th, 2018). The methods for

88   developing EMERGE have been previously published.(30) Briefly, a steering committee comprised of

89   7 members of ESPACOMP (SDG, LLZ, JDJ, RH, DAH, IBW, BV) led the project. The committee first

90   convened in Prague, Czech Republic in 2015, followed by 4 feedback rounds via email and

91   conference calls in 2016. Their discussion of a literature review of published adherence guidelines

92   and a further review of existing health research reporting guidelines(21-23, 31) yielded an initial pool

93   of 26 items (i.e., statements) organized according to the sections of the most used health research

94   reporting guidelines (i.e., CONSORT, STROBE). To avoid redundancy and facilitate EMERGE's

95   applicability across the various study designs, the committee considered overlap with existing

96   guidelines throughout the development process.(30)

97   The initial 26-item pool was the basis of two rounds of reactive e-Delphi surveys.(32, 33) A purposive

98   sample of 45 international experts (across 15 countries, 6 continents), representing diverse

99   disciplines and fields engaged in medication adherence research was selected and invited to

100   participate (i.e., 17 in clinical research, 14 in health services research, 13 in public health, 11 in

101   medicine, 9 in behavioral medicine/health psychology, 6 in journal editing, 5 in health policy, 5 in

102   pharmacoepidemiology, 5 in statistics, 4 in nursing, 4 in pharmacy / pharmaceutical sciences, 3 in

103   clinical pharmacology, 2 in the pharmaceutical industry and 6 in other fields; on average, experts

104   belonged to about 4 disciplines). Of the 45 experts, 29 participated in the first round (64% response

105   rate). They evaluated each item for relevance and clarity, and could comment, suggest further items

106   and/or modify the initial items. Guided by pre-defined rules(30) as well as by qualitative comments

107   received from the survey experts, the steering committee reviewed and discussed the first-round e-

108   Delphi results during a meeting in Húsafell, Iceland in July 2016.

109   Based on the agreed criteria, all 26 items initially evaluated in the first Delphi round were judged

110   relevant (mean 91%, SD 5%, range: 79%-97%) and clear (mean 84%, SD 10% range: 59%-97%).

111   Nevertheless, the experts' qualitative comments and subsequent discussion in the steering

112   committee presented opportunities to optimize the wording of several items. The committee

113   consequently chose to exclude 5 items due to redundancy or inconsistency with other EMERGE

114   items, or with items from the main reporting guidelines.

115   The remaining 21 items entered the second e-Delphi round, during which 26 of the 29 (90%) experts

116   who participated in the first round re-rated the items for relevance and clarity. All items again

117   cleared the threshold for relevance (mean 93%, range: 85%-100%) and clarity (mean 90%, range:

118   73%-100%). The qualitative comments allowed fine-tuning of several items' wording, resulting in the

119   21-item list presented at the annual ESPACOMP conference in Lisbon, Portugal in November 2016

120   and approved by a formal vote of all members.

121   **ESPACOMP MEDICATION ADHERENCE REPORTING GUIDELINE (EMERGE)**

122   EMERGE consists of 21 items organized in 2 sections (see table 1). The first section includes 4 items

123   outlining the *minimum reporting criteria* for medication adherence research. The following criteria

124   need to be specified clearly: (1) each phase of medication adherence studied (i.e., initiation,

125   implementation, persistence); (2) a precise operational/working definition of each of the phases of

126   medication adherence examined; (3) the methods of adherence measurement used for each phase,

127   along with information on performance of the measure (i.e., validity, reliability, potential bias); and

128   (4) the results of the analysis relevant to each phase.

129   The second section of the guideline consists of 17 items that provide more detailed and specific

130   information on the reporting of medication adherence. These are organized according to the

131   reporting guidelines for experimental and observational studies (i.e., CONSORT, STROBE) (table 1).

132   Building on the minimum reporting criteria, these items further highlight the importance of

133   considering and distinguishing between the 3 phases of medication adherence (e.g., item 6:

134   background/introduction; item 8: study objectives or hypotheses; item 15: statistical analysis; items

135   19 & 21: discussion). Other items address areas that are often under- or unreported in adherence

136   research. Item 7, for instance, addresses the need to clarify the rationale and/or framework guiding

137   the study. Item 9 addresses information relevant to the setting where the adherence study was

138   conducted (e.g., relevant characteristics of the healthcare system, healthcare organization and

139   healthcare team); and item 11 requests information on routine care related to the management of

140   medication adherence. For intervention studies (item 13), descriptions of both intervention and

141   comparator groups are requested. Interventions should be described (if relevant) in the context of

142   specified levels of the healthcare system (i.e., patient/caregiver, healthcare provider, healthcare

143   organization and healthcare system). Further methodological details are requested pertaining to

144   sampling (item 10 asks whether medication adherence is an eligibility criterion) and measurement

145 (item 12 addresses the potential impact of the adherence measure used on medication adherence).

146 Information requested on statistical methods distinguishes between medication adherence as an

147 outcome measure (item 15) and its use as an explanatory variable (item 16). Item 14 – an item

148 relevant to implementation science – asks for information (when applicable) on any implementation

149 strategy(34) that contributes to translation of a medication adherence intervention into clinical

150 practice. EMERGE also reminds authors to include details in their results sections of possible links

151 between non-participation and/or dropout either with medication non-adherence (item 17) or with

152 sample characteristics relevant to it (item 18).

153   [Please insert Table 1 here]

154 **DISCUSSION**

155 The ESPACOMP Medication Adherence Reporting Guideline (EMERGE) was developed to help

156 researchers improve the quality of their reporting of medication adherence research, as this type of

157 research is often methodologically weak (8, 35, 36) and suboptimally reported (11-13). While

158 EMERGE has the advantage of being applicable to multiple study designs and methods focusing on

159 medication adherence, its use will involve authors combining EMERGE items with other appropriate

160 guidelines for health research reporting (e.g., STROBE, CONSORT, STaRi).

161 EMERGE was developed through a consensus-based process involving a multidisciplinary group of

162 international medication adherence experts. Using the Delphi surveys, these experts provided two

163 rounds of feedback on the relevance and clarity of each included item. In addition to enhancing

164 EMERGE's relevance across diverse settings, their cooperation will facilitate guideline

165 implementation.

166 One of EMERGE's major strengths is its grounding in a medication adherence conceptualization

167 provided by a robust taxonomy.(10) Since its initial publication, this taxonomy, distinguishing

168 between 3 phases of adherence (i.e., initiation, implementation, persistence), has greatly benefitted

169 the field of medication adherence research,(37, 38) and has been broadly adopted and widely

170 cited.(39) EMERGE highlights the need to acknowledge and specify each of these 3 phases as being

171 distinct parts of the process by which patients manage their medication regimens, that require

172 specific considerations regarding their conceptualization, definition, measurement and analysis.

173 EMERGE items – with the 4 minimum reporting criteria at their core – reflect essential yet often

174 poorly handled or omitted elements of medication adherence research reporting. This includes the

175 omission or suboptimal definition of key terms,(7, 11-13) the use of suboptimal measures,(15) and

176 the use of inappropriate analytical methods.(11-13) EMERGE also highlights the need for other

177 relevant and often neglected aspects of adherence research reporting, e.g., a clearly-explained
178 rationale or framework(16) and detailed information on the healthcare setting, including routine
179 care.(15)

180 EMERGE includes an item relevant to implementation science which is complementary to the STaRi
181 reporting guideline,(23) in recognition of the importance of this discipline in advancing the field of
182 medication adherence. While several promising interventions have been developed to improve
183 adherence,(8, 35, 40) none have proved easy to implement in clinical practice. We do not suggest
184 that every study can or should include an implementation component, but encourage researchers to
185 plan studies with an eye towards potential implementation and sustainability.

186 The main limitation affecting EMERGE's development process is its primary focus on quantitative
187 methodologies. However, the 4 minimum reporting criteria can also support qualitative and mixed-
188 methods research in guaranteeing that the research's focus and relevant methodological aspects are
189 aligned with the adherence taxonomy.(10) Additionally, although initial user testing demonstrated
190 its easy applicability in combination with the main reporting guidelines, the advised combination of
191 EMERGE with other reporting guidelines might initially seem challenging. Moreover, while following
192 the 21 EMERGE items will yield thorough reporting of all matters common to medication adherence
193 research, journal word count limits may sometimes restrict full reporting. Possible solutions include
194 pre-publishing detailed methodologies and protocols and/or providing online-only
195 supplements/appendices. Finally, although efforts were made to guarantee representation of all
196 continents, there were fewer people from African and Asian countries in the international Delphi
197 expert team.

198 In addition to this article, dissemination and use of the EMERGE guidelines will be enhanced by
199 information available on the EQUATOR webpage (www.equator-network.org, accessed: April 30th,
200 2018) and the ESPACOMP website (www.espacomp.eu/emerge, accessed: April 30th, 2018), and
201 endorsed by a range of related journals and professional organizations. ESPACOMP will support
202 regular updates of EMERGE to ensure timely propagation of lessons learned from its use, along with
203 new developments in medication adherence science.

CONCLUSION

205 Implementation of ESPACOMP Medication Adherence Reporting Guideline (EMERGE) is expected to
206 enhance the quality of medication adherence research reporting via standardization, reducing
207 research waste, accelerating progress in this and related fields, and ultimately, improving patient
208 outcomes.

209 **ROLE OF THE FUNDING SOURCE**

210 The study was funded by ESPACOMP. As the EMERGE steering committee is composed entirely of

211 ESPACOMP members, they took the sole lead in designing EMERGE, in writing this paper, and in

212 submitting it for publication.

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TABLE 1: ESPACOMP Medication Adherence Reporting Guideline (EMERGE)

Section	Item No	Recommendation	Reported on page No. / line No.
Minimum reporting criteria			
	1a	**Phases of medication adherence**: State the phase(s) of medication adherence studied (i.e. initiation, implementation, or persistence) and justify, where possible, the reasons the study focuses on the chosen phase(s).	……
	1b	**Operational definition**: Provide the precise operational/working definition for each (of the) phase(s) of medication adherence studied (i.e., initiation, implementation, or persistence).	……
	1c	**Measurement**: Specify the method(s) of medication adherence measurement (e.g., self-report, claims data, blood sampling, electronic monitoring). Consider each phase studied (i.e., initiation, implementation, or persistence), with details on the performance of the measure(s) (e.g., validity, reliability, potential bias), where applicable.	……
	1d	**Results**: Describe the results of the analysis appropriate to each (of the) phase(s) of medication adherence studied (i.e., initiation, implementation, or persistence).	……
Abstract			
	2a	Present in the abstract, in as much detail as space permits, information on the 4 minimum reporting criteria (i.e., items 1.1 - 1.4).	……
Background/introduction			
	3a	Summarize what is known about the topic with appropriate reference to the phase(s) of medication adherence (i.e., initiation, implementation, and persistence).	……
	3b	Describe the rationale and/or framework guiding the medication adherence study (e.g., theoretical framework, implementation science model).	……

Study objectives or hypotheses

	4a	State the study objectives or hypotheses with reference to the phase(s) of medication adherence studied and context (patient population and setting).	……

Methods

|			
Design & participants	5a	Describe the setting in which the study was conducted. Refer to factors relevant to medication adherence, such as characteristics of the healthcare system, the healthcare organization, and the healthcare team.	……
	5b	State whether medication adherence was an eligibility criterion (e.g., inclusion/exclusion). If so, define the measures and rules used.	……
	5c	Describe routine care related to the management of medication adherence (e.g., routine assessment of medication adherence, adherence support programs, provider training), if applicable.	……
Measurement		*PLEASE REFER TO ITEM 1.C. IN ADDITION TO THE "MEASUREMENT" ITEM BELOW*	
	6a	Measurement methods can themselves impact medication adherence (e.g., questionnaires, blood sampling, electronic monitoring). Address this problem as appropriate.	……
Intervention (where applicable)	7a	For intervention and comparator groups, describe each relevant level of the medication adherence intervention (e.g., healthcare system, healthcare organization, healthcare provider, patient/caregiver).	……
	7b	Describe any implementation strategy that contributes to the translation (e.g., uptake, delivery, sustainability) of the medication adherence intervention in clinical practice, if applicable.	……
Statistical analysis	8a	If medication adherence is an outcome variable, justify the statistical methods, given the characteristics of the variable (e.g., phases of medication adherence, data type, statistical distribution, data censoring, longitudinal dependence).	……
	8b	If medication adherence is an explanatory variable, describe how it is related to the outcome(s) (e.g., causal pathway, temporal sequence).	……

Results			
		PLEASE REFER TO ITEM 1.D IN ADDITION TO THE "RESULTS" ITEMS BELOW	
	9a	Determine whether non-participation and/or dropout are associated with non-adherence, and provide any relevant data.	……
	9b	Present sample characteristics relevant to medication adherence (e.g., socio-demographic, therapy-related, condition-related, patient-related, caregiver-related, healthcare team/healthcare system-related).	……
Discussion			
	10a	Discuss study strengths and limitations with reference to the phase(s) of medication adherence, where applicable (i.e., initiation, implementation, persistence).	……
	10b	Discuss the study findings in the context of existing medication adherence evidence (e.g., theory, measurement, intervention effects).	……
	10c	Discuss the generalizability (external validity) of the study findings with reference to the phase(s) of medication adherence, where applicable (i.e., initiation, implementation, persistence).	……
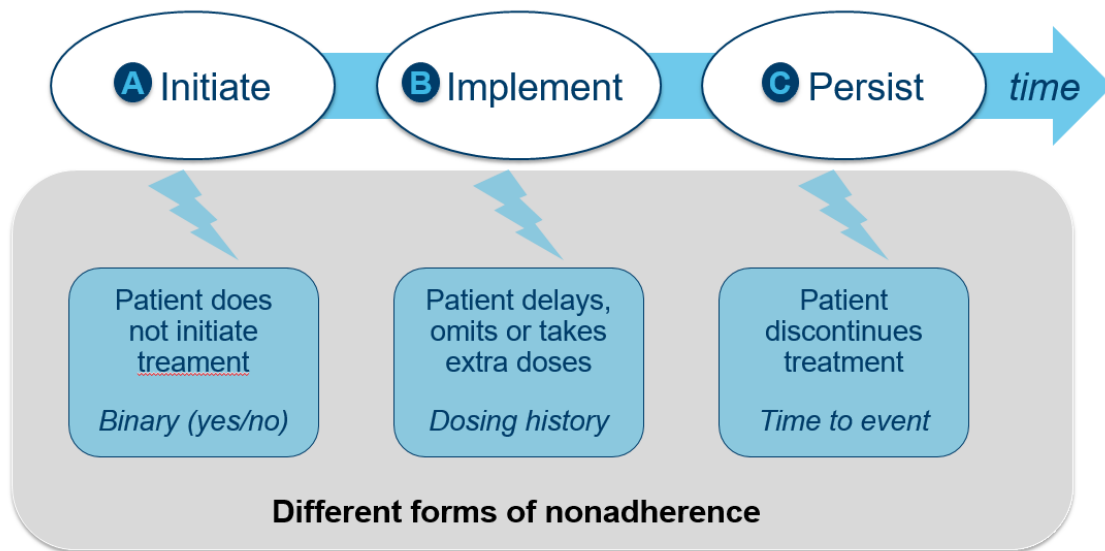
Based on Vrijens et al. 2012. Br J Clin Pharmacol.(10)

FIGURE 1: Conceptualization of medication adherence