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ESPACOMP Medication Adherence Reporting Guideline (EMERGE)

Sabina De Geest, Leah L Zullig, Jacqueline Dunbar-Jacob, Remon Helmy, Dyfrig A Hughes, Ira B Wilson*, Bernard Vrijens*

*Joint last authorship

Sabina De Geest, PhD, RN: Professor, Nursing Science, Chair Department of Public Health, Faculty of Medicine, University of Basel, 4056 Basel, Switzerland & Professor. Academic Centre for Nursing and Midwifery, Department of Public Health and Primary Care, KU Leuven, 3000 Leuven, Belgium

Leah L Zullig, PhD, MPH: Assistant Professor, Center for Health Services Research in Primary Care, Durham Veterans Affairs Health Care System, Durham, North Carolina 27701, USA & Department of Population Health Sciences, School of Medicine, Duke University, Durham, North Carolina 27707, USA

Jacqueline Dunbar-Jacob, PhD, RN: Distinguished Service Professor & Dean. School of Nursing, University of Pittsburgh, Pittsburgh, 3500 Victoria Building, Pittsburgh PA 15261, USA

Remon Helmy, MSc: Research assistant, Nursing Science, Department of Public Health, Faculty of Medicine, University of Basel, 4056 Basel, Switzerland

Dyfrig A Hughes, MRPharmS, PhD: Professor and co-director. Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, Gwynedd, North Wales LL57 2PZ, UK

Ira B Wilson, MD, PhD: Professor and Chair. Department of Health Services, Policy & Practice, Brown University School of Public Health, Providence, Rhode Island 02912, USA

Bernard Vrijens, PhD: Invited professor. Department of Public Health, University of Liège, 4000 Liège, Belgium & Chief science officer. AARDEX Group, 4600 Visé, Belgium

Correspondence and reprint request to: Sabina De Geest, Nursing Science, Department of Public Health, Faculty of Medicine, University of Basel, 4056 Basel, Switzerland Tel: +41 79 3741081; Fax: +41 61 2070951; Email: sabina.degeest@unibas.ch

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ABSTRACT

Medication adherence-related research applies observational, interventional and/or implementation science approaches spanning multiple disciplines to assess or manage medication adherence. This demands coherent conceptualization, valid methods, appropriate analyses, and complete, accurate reporting. To ensure reliable reporting, the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE) recommends standard reporting approaches based on an accepted taxonomy.

This guideline results from a literature review, a reactive e-Delphi study with 26 international multidisciplinary medication adherence experts, and feedback from the ESPACOMP membership. It is designed to supplement existing guidelines for health research reporting, and structured around 4 minimum reporting criteria and 17 items reflecting best reporting practice. By enhancing and harmonizing research reporting, EMERGE aims to advance research and, ultimately, patient outcomes.

CHALLENGES AND SHORTCOMINGS IN MEDICATION ADHERENCE REPORTING

Medication non-adherence is a major public health problem(1, 2) with significant health and economic consequences.(1-4) For many conditions, taking medications as prescribed is crucial to achieve optimal outcomes.(5-7) Despite more than 50 years of research, the evidence base for effective interventions that can be implemented in routine clinical care remains limited.(8, 9)

Medication adherence-related research applies observational, interventional and/or implementation science approaches across disciplines including, but not limited to medicine, pharmacy, nursing, behavioral science, sociology, pharmacometrics, biostatistics and health economics.(10) Unfortunately, inadequate research reporting often hampers interpretation of findings, complicates data abstraction for meta-analyses and prevents study replication. Common problems of reporting include unclear, inconsistent definitions;(11-14) inadequate measurement of adherence outcomes;(7, 14, 15) suboptimal methods of analysis;(11-14) insufficiently detailed descriptions of intervention delivery settings;(15) and scant theoretical underpinnings.(16)

Previous efforts to improve adherence research reporting standards(11, 17-20), have resulted in guidelines and recommendations that overlap with existing health research reporting guidelines, e.g., CONsolidated Standards of Reporting Trials (CONSORT),(21) STrengthening the Reporting of OBservational studies in Epidemiology (STROBE),(22) Standards for Reporting Implementation Studies (StaRI) Statement (StaRI).(23) These recommendations only indirectly pertain to medication adherence research,(17, 19) include no clear conceptualization of medication adherence(11, 17, 19, 20) and focus on research methods rather than reporting.(11, 19, 20)

Weighing these shortcomings against evidence that guidelines endorsed by professional societies and journals enhance overall health research reporting,(24-28) the European Society for Patient Adherence, COMpliance, and Persistence (ESPACOMP, www.espacomp.eu, accessed: April 30th, 2018) developed the ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Grounded in the conceptualization of medication adherence provided by the previously-reported taxonomy,(10) EMERGE aims to complement existing health research reporting guidelines, increasing the transparency and consistency of reporting by guiding researchers through processes specifically relevant to medication adherence, as well as to those for which it is a variable of interest.

Taxonomy for medication adherence

EMERGE adopts the previously-reported taxonomy(10) which defines medication adherence as "the process by which patients take their medications as prescribed," consisting of three interrelated yet distinct phases: (A) **initiation**; (B) **implementation;** and (C) **persistence (figure 1).** Non-adherence to

medications can occur in any of these phases, e.g., late, incomplete, or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen (e.g., late, skipped, extra or reduced doses, drug holidays) or early discontinuation (non-persistence). Each phase poses different methodological challenges related to how medication use is operationally defined, measured, and analyzed.

DEVELOPMENT OF EMERGE

EMERGE was developed in accordance with recommendations for health research reporting guideline developers(29) of the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network (www.equator-network.org, accessed: April 30th, 2018). The methods for developing EMERGE have been previously published.(30) Briefly, a steering committee comprised of 7 members of ESPACOMP (SDG, LLZ, JDJ, RH, DAH, IBW, BV) led the project. The committee first convened in Prague, Czech Republic in 2015, followed by 4 feedback rounds via email and conference calls in 2016. Their discussion of a literature review of published adherence guidelines and a further review of existing health research reporting guidelines(21-23, 31) yielded an initial pool of 26 items (i.e., statements) organized according to the sections of the most used health research reporting guidelines (i.e., CONSORT, STROBE). To avoid redundancy and facilitate EMERGE's applicability across the various study designs, the committee considered overlap with existing guidelines throughout the development process.(30)

The initial 26-item pool was the basis of two rounds of reactive e-Delphi surveys.(32, 33) A purposive sample of 45 international experts (across 15 countries, 6 continents), representing diverse disciplines and fields engaged in medication adherence research was selected and invited to participate (i.e., 17 in clinical research, 14 in health services research, 13 in public health, 11 in medicine, 9 in behavioral medicine/health psychology, 6 in journal editing, 5 in health policy, 5 in pharmacoepidemiology, 5 in statistics, 4 in nursing, 4 in pharmacy / pharmaceutical sciences, 3 in clinical pharmacology, 2 in the pharmaceutical industry and 6 in other fields; on average, experts belonged to about 4 disciplines). Of the 45 experts, 29 participated in the first round (64% response rate). They evaluated each item for relevance and clarity, and could comment, suggest further items and/or modify the initial items. Guided by pre-defined rules(30) as well as by qualitative comments received from the survey experts, the steering committee reviewed and discussed the first-round e-Delphi results during a meeting in Húsafell, Iceland in July 2016.

Based on the agreed criteria, all 26 items initially evaluated in the first Delphi round were judged relevant (mean 91%, SD 5%, range: 79%-97%) and clear (mean 84%, SD 10% range: 59%-97%). Nevertheless, the experts' qualitative comments and subsequent discussion in the steering

committee presented opportunities to optimize the wording of several items. The committee consequently chose to exclude 5 items due to redundancy or inconsistency with other EMERGE items, or with items from the main reporting guidelines.

The remaining 21 items entered the second e-Delphi round, during which 26 of the 29 (90%) experts who participated in the first round re-rated the items for relevance and clarity. All items again cleared the threshold for relevance (mean 93%, range: 85%-100%) and clarity (mean 90%, range: 73%-100%). The qualitative comments allowed fine-tuning of several items' wording, resulting in the 21-item list presented at the annual ESPACOMP conference in Lisbon, Portugal in November 2016 and approved by a formal vote of all members.

ESPACOMP MEDICATION ADHERENCE REPORTING GUIDELINE (EMERGE)

EMERGE consists of 21 items organized in 2 sections (see table 1). The first section includes 4 items outlining the *minimum reporting criteria* for medication adherence research. The following criteria need to be specified clearly: (1) each phase of medication adherence studied (i.e., initiation, implementation, persistence); (2) a precise operational/working definition of each of the phases of medication adherence examined; (3) the methods of adherence measurement used for each phase, along with information on performance of the measure (i.e., validity, reliability, potential bias); and (4) the results of the analysis relevant to each phase.

The second section of the guideline consists of 17 items that provide more detailed and specific information on the reporting of medication adherence. These are organized according to the reporting guidelines for experimental and observational studies (i.e., CONSORT, STROBE) (table 1). Building on the minimum reporting criteria, these items further highlight the importance of considering and distinguishing between the 3 phases of medication adherence (e.g., item 6: background/introduction; item 8: study objectives or hypotheses; item 15: statistical analysis; items 19 & 21: discussion). Other items address areas that are often under- or unreported in adherence research. Item 7, for instance, addresses the need to clarify the rationale and/or framework guiding the study. Item 9 addresses information relevant to the setting where the adherence study was conducted (e.g., relevant characteristics of the healthcare system, healthcare organization and healthcare team); and item 11 requests information on routine care related to the management of medication adherence. For intervention studies (item 13), descriptions of both intervention and comparator groups are requested. Interventions should be described (if relevant) in the context of specified levels of the healthcare system (i.e., patient/caregiver, healthcare provider, healthcare organization and healthcare system). Further methodological details are requested pertaining to sampling (item 10 asks whether medication adherence is an eligibility criterion) and measurement

(item 12 addresses the potential impact of the adherence measure used on medication adherence). Information requested on statistical methods distinguishes between medication adherence as an outcome measure (item 15) and its use as an explanatory variable (item 16). Item 14 – an item relevant to implementation science – asks for information (when applicable) on any implementation strategy(34) that contributes to translation of a medication adherence intervention into clinical practice. EMERGE also reminds authors to include details in their results sections of possible links between non-participation and/or dropout either with medication non-adherence (item 17) or with sample characteristics relevant to it (item 18).

[Please insert Table 1 here]

DISCUSSION

The ESPACOMP Medication Adherence Reporting Guideline (EMERGE) was developed to help researchers improve the quality of their reporting of medication adherence research, as this type of research is often methodologically weak (8, 35, 36) and suboptimally reported (11-13). While EMERGE has the advantage of being applicable to multiple study designs and methods focusing on medication adherence, its use will involve authors combining EMERGE items with other appropriate guidelines for health research reporting (e.g., STROBE, CONSORT, STaRi).

EMERGE was developed through a consensus-based process involving a multidisciplinary group of international medication adherence experts. Using the Delphi surveys, these experts provided two rounds of feedback on the relevance and clarity of each included item. In addition to enhancing EMERGE's relevance across diverse settings, their cooperation will facilitate guideline implementation.

One of EMERGE's major strengths is its grounding in a medication adherence conceptualization provided by a robust taxonomy.(10) Since its initial publication, this taxonomy, distinguishing between 3 phases of adherence (i.e., initiation, implementation, persistence), has greatly benefitted the field of medication adherence research,(37, 38) and has been broadly adopted and widely cited.(39) EMERGE highlights the need to acknowledge and specify each of these 3 phases as being distinct parts of the process by which patients manage their medication regimens, that require specific considerations regarding their conceptualization, definition, measurement and analysis.

EMERGE items – with the 4 minimum reporting criteria at their core – reflect essential yet often poorly handled or omitted elements of medication adherence research reporting. This includes the omission or suboptimal definition of key terms,(7, 11-13) the use of suboptimal measures,(15) and the use of inappropriate analytical methods.(11-13) EMERGE also highlights the need for other

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

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

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

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

CONCLUSION

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

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The study was funded by ESPACOMP. As the EMERGE steering committee is composed entirely of ESPACOMP members, they took the sole lead in designing EMERGE, in writing this paper, and in submitting it for publication.

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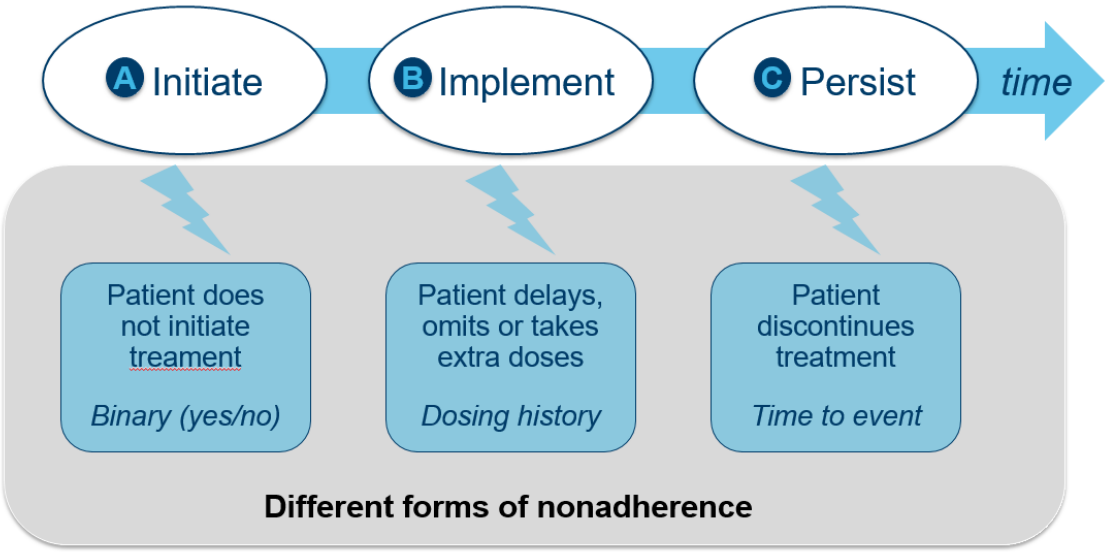
TABLE 1: ESPACOMP Medication Adherence Reporting Guideline (EMERGE)

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