The need for patient adherence standard measures for Big Data.

Przemyslaw Kardas, Isabel Aguilar-Palacio, Marta Almada, Caitriona Cahir, Elísio Costa, Anna Giardini, Sara Malo, Mireia Massot Mesquida, Enrica Menditto, Luis Midão, Carlos Luis Parra-Calderón, Enrique Pepiol Salom, Bernard Vrijens

Submitted to: Journal of Medical Internet Research
on: February 08, 2020

Table of Contents

The need for patient adherence standard measures for Big Data.

Przemyslaw KardasProf Dr, ; Isabel Aguilar-Palacio; Marta Almada; Caitriona Cahir; Elísio Costa; Anna Giardini; Sara Malo; Mireia Massot Mesquida; Enrica Menditto; Luis Midão; Carlos Luis Parra-Calderón; Enrique Pepiol Salom; Bernard Vrijens

Corresponding Author:
Przemyslaw KardasProf Dr,
Email: pkardas@csk.am.lodz.pl

Abstract

Despite half a century of dedicated studies, medication adherence remains far from perfect, with many patients not taking their medications as prescribed. The magnitude of this problem is rising, jeopardizing the effectiveness of evidence-based therapies. An important reason for this is the unprecedented demographic change at the beginning of 21st century. Ageing leads to multimorbidity and complex therapeutic regimens that create fertile ground for non-adherence. As this scenario is a global problem, it needs a worldwide answer. Might we find this answer thanks to new opportunities created by the digitization of healthcare?

Day by day health-related information is collected in electronic health records, pharmacy dispensing databases, health insurance systems and national health system records. These Big Data repositories offer an unprecedented opportunity to study adherence both retrospectively and prospectively, at the population level, as well as its related factors. If only we had widely accepted standard measures of adherence, we could use this data to inform health research, clinical practice and public health. These standards could also help us to better understand the relationship between adherence and clinical outcomes, and allow for fair benchmarking of effectiveness and cost-effectiveness of adherence-targeting interventions.

Unfortunately, despite this obvious need, we are still far from having sound standards of formatting, and analyzing Big Data in order to assess, uniformly present and compare patterns of medication adherence across studies. The aim of this paper is to call for producing such consensus standards, in order to help adherence, and make healthcare systems more effective and sustainable.

(JMIR Preprints 08/02/2020:18150)
DOI: https://doi.org/10.2196/preprints.18150

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

The need for patient adherence standard measures for Big Data.

Abstract

Despite half a century of dedicated studies, medication adherence remains far from perfect, with many patients not taking their medications as prescribed. The magnitude of this problem is rising, jeopardizing the effectiveness of evidence-based therapies. An important reason for this is the unprecedented demographic change at the beginning of 21st century. Ageing leads to multimorbidity and complex therapeutic regimens that create fertile ground for non-adherence. As this scenario is a global problem, it needs a worldwide answer. Might this answer be provided, given the new opportunities created by the digitization of healthcare?

Day by day health-related information is collected in electronic health records, pharmacy dispensing databases, health insurance systems and national health system records. These Big Data repositories offer a unique chance to study adherence both retrospectively and prospectively, at population level, as well as its related factors. In order to make the full use of this opportunity, there is a need to develop standardised measures of adherence, which can be applied globally to Big Data and will inform scientific research, clinical practice and public health. These standardized measures may also enable a better understanding of the relationship between adherence and clinical outcomes, and allow for fair benchmarking of effectiveness and cost-effectiveness of adherence-targeting interventions.

Unfortunately, despite this obvious need, such standards are still lacking. Therefore, the aim of this paper is to call for producing a consensus on global standards for measuring adherence with Big Data. More specifically, sound standards of formatting, and analysing Big Data are needed in order to assess, uniformly present and compare patterns of medication adherence across studies. Wide use of these standards may improve adherence, and make healthcare systems more effective and sustainable.

List of abbreviations:

ABC – Ascertaining Barriers for Compliance project, AI - Artificial Intelligence, EIP on AHA - European Innovative Partnership on Active and Healthy Ageing, EHR - electronic health record, EMA - European Medicines Agency, EMERGE – ESPACOMP Medication Adherence Reporting Guideline, ESPACOMP - International Society for Medication Adherence, HMA - Heads of

Medicines Agencies, ISO - International Organization for Standardization, ISPOR - International Society for Pharmacoeconomics and Outcomes Research, IT - Information Technology, MPR - medication possession ratio, PDC - proportion of days covered, WHO - World Health Organization

Introduction

Despite half a century of dedicated studies, medication adherence remains far from perfect. In fact, non-adherence to medication - i.e. the scenario in which the patients are not taking their medications as prescribed - is still very prevalent. According to the World Health Organization (WHO), 50% of patients are estimated to deviate from their chronic treatments [1]. Jeopardizing the effectiveness of evidence-based therapies, it has been shown to lead to poor health outcomes, increased use of health services and increased costs (both direct, as well as indirect e.g. due to absenteeism, lost productivity etc.) [2]. In a recent meta-analysis, medication non-adherence has been found to be significantly associated with all-cause hospitalization and mortality in older people [3]. Thus, non-adherence is an important determinant of individual health. On population level, it also seriously affects public health, and the economy. Due to this all, non-adherence has been recognized by WHO as a “problem of striking magnitude” [1].

Unfortunately, the seriousness of this problem is ever increasing. An important reason for this is the unprecedented demographic change that is taking place at the beginning of 21st century. It affects the whole world, and is particularly pronounced in Europe. According to Eurostat, currently, persons aged 65 years and older comprise 20% of EU-28 population and this proportion is expected to rise up to 31% by 2100. Even more striking are the statistics for very old citizens – those aged 80+ are expected to rise within the same time period from current 6% of EU-28 population to 15%. [4]

Longer lifespan results in an increase in the prevalence of non-communicable chronic conditions and multimorbidity (usually defined as the coexistence of two or more chronic conditions in an individual). This, in turn, leads to the frequent use of complex therapeutic regimens and creates fertile ground for non-adherence. [5].

In order to prevent non-adherence, one needs to know the major drivers of this phenomenon. The WHO developed a model of the determinants affecting adherence and grouped them into five main sets of factors: health system related factors, therapy related

factors, condition related factors, patient related factors, and socioeconomic factors [1]. Based on this model of adherence, multiple non-adherence-targeting interventions have been designed and tested but unfortunately only few have been successful. As stated in a recent Cochrane systematic review, “current methods of improving medication adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized”. [6].

Indeed, medication taking is a complex behaviour, and diverse determinants play different roles at the individual level. In a consequence, it seems to be unrealistic to expect that one uniform intervention will solve the problem of non-adherence in each and every case. On the other hand, there is a rising body of evidence that non-adherence could be effectively managed through the use of various innovative digital solutions [7]. Successful examples include web-based education and monitoring programs [8], clinical decision support systems using data from Electronic Health Records (EHRs) to produce alerts [9], mobile technologies (mHealth) and dedicated apps providing various combinations of patient monitoring, education, and facilitation of adherence [10,11], etc. Thanks to digitization, for the first time in the history, non-adherence may also become precisely measurable on a mass scale, due to the availability of large health care databases. This is particularly important for older populations, which is a group usually understudied in clinical trials for various reasons (e.g. multimorbidity and related polymedication).

However, these promising opportunities are not fully utilized yet due to the lack of basic widely accepted standards for measuring and managing adherence in Big Data. The discussion that started in 2019 at the forums of professional bodies active at the area of patient adherence research, i.e. Action Group A1 ‘Adherence to prescription and medical plans’ of the European Innovative Partnership on Active and Healthy Ageing (EIP on AHA) and International Society for Medication Adherence ESPACOMP, to which the authors of this publication belong, led to the conclusion that this scenario needs to be changed. This idea corresponds very well with recent recommendations of the HMA-EMA joint Big Data Task Force, which called for the development of skills and the creation of capabilities to analyse Big Data [12]. Therefore, the aim of this publication is to establish a call for producing a consensus on global standards for measuring adherence with Big Data. More specifically, sound standards of formatting, and analysing Big Data are needed in order to assess, uniformly present and compare patterns of medication adherence across studies, and thus, help scientific research, clinical practice, and public health.

Opportunities created for adherence due to digitization of the healthcare sector

Digitization is a new opportunity that has, in recent times, become more frequently adopted in the healthcare sector. Interestingly to date, digital solutions have been widely used outside healthcare, but only recently have they have become employed in the field of medicine and offer great promise towards improved and more efficient care. In order to speed up this process, in 2018 the European Commission developed a plan for the digital transformation of health and care in the Digital Single Market. The plan is based on three pillars; (i) secure data access and sharing; (ii) connecting and sharing health data for research, faster diagnosis and improved individualized healthcare services and health outcomes and; (iii) strengthening citizen empowerment and individual care through digital services [13]. This plan is a part of the overarching European Strategy for Data [14]. Digitization of the healthcare sector creates an opportunity for using Big Data analytics tools and methods to assess non-adherence, improve clinical practice/healthcare services and promote the use of tailored interventions. Routinely collected information on prescribing and dispensing which are available in electronic health records, pharmacy dispensing databases, health insurance claims systems, and national health systems records, enables a more thorough exploration of the relationship between adherence and health outcomes. The rising use of mHealth by patients for self-monitoring and disease management is also another potential data source for analysing. Thus, Big Data may represent a powerful and relatively low-cost resource for investigating important public health concerns in real-life scenarios: prevalence of non-adherence, its drivers and the consequences of non-adherence. Big Data can also be used to provide information for designing new interventions, targeting both prevention and management of non-adherence. Moreover, Big Data allows research on an incomparable scale, covering large populations (e.g. primary non-adherence - a measure of unfilled prescriptions - was recently assessed in a cohort of 1.6 million Catalonian primary care patients [15], and in a national population based study in Poland [16]). Unlike medical trials, Big Data also provides the opportunity to assess adherence longitudinally (e.g. an Estonian study analysed a national database over a period of 15 years [17]). All this is possible without typical limitations in terms of costs, intrusiveness or bias, which are characteristic of studies employing other sorts of data for adherence measurement and monitoring. However, at present uniform and accepted

standards of adherence measurement for Big Data are still lacking. Moreover, currently Big Data collections are not uniformly formatted nor structured for adherence measurement, which means that non-trivial operations are needed to allow for this kind of analysis. Therefore, to build a solid evidence base for adherence management across clinical settings, it is necessary to standardize adherence estimation and facilitate the appropriate use of these standards [18].

Adherence research is not the only area of research to face problems with standardization, when it comes to digital health. For example, there are no global standards for EHR still. [19] Various historical, cultural, economic and political reasons could be citied as causative factors that despite activities of several interoperability initiatives, both public and private, this is still the case [20]. Several Standardization Development Organizations have developed very mature and widely implemented standards such as the CDA [21] and FHIR [22] by HL7, and CEN-ISO 13606 [23], but they are limited in their interoperability. Interestingly, ISO 10781:2015 provides a reference list of functions that may be present in an Electronic Health Record System, of which one tackles adherence assessment: Care Patient Support CPS 3.1 Function on “Support for Standard Assessments”. [24]

A systemic review of the challenges toward the use of Big Data in healthcare identified issues of data structure, security, data standardization, storage and transfers, and managerial skills such as data governance to be those most often provided in the current literature [25]. Practical challenges include data pre-processing and curation, model training, refinement of the systems, ethical and legal issues, data privacy and security, end-users understanding acceptance, and much more [26, 27].

Certainly, to overcome all these challenges is not easy. However, it is quite easy to illustrate why this scenario urgently needs to be changed.

Need for standard Big Data-related adherence metrics for research

The introduction of the ABC taxonomy and new adherence terminology (named after dedicated European research project ‘*Ascertaining Barriers for Adherence’*) made the first big step forward in terms of standardization, by defining three essential components of adherence. These components are: (i) initiation (taking the first dose of prescribed medication); (ii) implementation (taking medication as prescribed); and (ii) discontinuation

(stopping treatment) [28]. Following this, the recently introduced EMERGE guideline (*ESPACOMP Medication Adherence Reporting Guideline* developed under umbrella of International Society for medication adherence ESPACOMP) provides guidance, along with a checklist for reporting results of studies on medication adherence [29]. Other interesting activities in this area include the work initiated with the support of the Government of Spain and the European project StandICT.eu to generate an extension of the Snomed CT terminology for the domain of adherence [30], and the proposal to include terms of adherence in the amendment to ISO 13940 (System of concepts to support continuity of care) currently in progress in ISO TC 215 [31].

However, there are still many challenges with the use of Big Data for adherence assessment. Without standard metrics, the same data may lead to diverse results, as clearly depicted by a study of Malo *et al*. which found different mean adherence values and proportions of adherent patients when using medication possession ratio (MPR) versus proportion of days covered (PDC) [32].

To date, numerous studies of adherence have been undertaken, using diverse approaches to data analysis, which have led to mixed results. Most often, pharmacy records are used to measure adherence in terms of implementation and discontinuation [33]. EHR data have also been used for effective prediction of medication adherence trajectories [34], which has evoked certain discussion [35]. Menditto *et al*. managed to integrate and analyse six databases from 3 countries, which allowed for a fair comparison of medication adherence across the various countries [36]. Another study managed to assess and compare adherence to chronic medication across three European cohorts of older people by developing a common protocol and using structured documents for sharing and applying methodologies [37].

Some attempts to introduce standards to adherence assessment in Big Data have also been made by ISPOR (International Society for Pharmacoeconomics and Outcomes Research). ISPOR Medication Adherence and Persistence Special Interest Group produced recommendations for assessment of initial medication adherence [38] and proposed a checklist for medication adherence studies using retrospective databases [39]. Arnet *et al*. [40]. as well as Raebel *et al.* [41] proposed standard definitions and their operationalization to quantify adherence to medication from electronic databases. Lehnman *et al*. [42] and Williams *et al*. [43] suggested some basic guidance regarding use of pharmacy refill data to assess adherence. At the same time, a systematic review of publications on adherence in

older Americans, identified as many as 20 differently named measures of adherence derived from pharmacy claims data [44]. Even more interestingly, some adherence measures derived from Big Data are already in use for incentivizing healthcare providers to consider long-term health outcomes. In the US, Centers for Medicare & Medicaid Services adopted several quality measures using the threshold of PDC≥0.8 for the drug(s) under measurement, for a period of 12 consecutive months [45]. In fact, there is evidence that this improves adherence [46].

Moreover, another important question that needs to be addressed in future standardized measures of adherence in Big Data is: what is the subject of adherence assessment: a drug, a condition, or a patient? In other words, how to measure adherence to multiple medications prescribed for the same condition, and/or to various conditions in patients with multimorbidity [47]. Indicators designed and widely used to evaluate single-medication adherence are not necessarily valid for assessment of adherence to polypharmacy regimens [48]. For example, a study assessing adherence in individuals belonging to the Epichron cohort returned highly diverse results for various drug classes: 72.4% for antidiabetics versus only 44.3% for lipid-lowering drugs [49]. A recent systematic review found serious inconsistency in the measures used to estimate adherence and persistence to multiple cardiometabolic medications [50], while another review concluded that ‘there appears to be no standardized method to measure multiple medication adherence’ [51]. For sure, further research is needed in this respect and is particularly important given the ageing population.

In summary the major disadvantage of the current lack of widely accepted standards for adherence assessment is the difficulty in comparing and interpreting scientific study results. Uniform adherence measurement and a common ontology urgently need to be developed, in order to support research and to enable real life implementation of study findings [40, 52, 53]. This is also necessary for cross-study comparisons and fair benchmarking of adherence-targeting interventions.

Need for standard Big Data-related adherence metrics for clinical practice, public health and health policy

Big Data and the development of a standardized measure of adherence may enable more

reliable and valid investigations into the association between non-adherence and health outcomes. To date there is no consensual standard for what constitutes adequate adherence. In practice, 80% is often used as a cut-off to classify “good adherence” but scientific evidence for this threshold is unclear. In fact, a systematic review investigated medication adherence thresholds in relation to clinical outcomes and found the included studies to be highly heterogeneous and could not confirm or reject the validity of the historical 80% cut off threshold for adherence [54]. Moreover, many treatments are also preventative and it may take a very long time to determine any therapeutic benefit at all from such treatments.

Various interventions have been designed in order to prevent and manage non-adherence in real life settings. Unfortunately, despite objective need, these interventions are generally underused. Lack of standardised comparable measures of adherence is one of the major barriers towards the objective selection of the most effective and cost-effective interventions [2], and the scaling-up of best practice. Only with reliable and valid measures, can non-adherence be tracked along a timeline, allowing the assessment of the long-term effects of particular interventions, and the benchmarking of their effectiveness. Standard measures and guidelines to assess adherence could also facilitate the introduction as well as the assessment of the effectiveness of incentives to promote adherence at the patient, provider and payers level and the ability to target individual risk factors at the various health care provider levels [55].

Standardized adherence measures employed to Big Data sets may also provide an insight into the reasons why patients do not adhere to their prescribed medication regimens. This is of utmost importance as a review of systematic reviews identified 771 individual factor items as possible determinants of non-adherence, concluding that “a lack of standardized adherence definitions and use of poor measurement methods resulted in many inconsistencies in the findings and many of the identified factors had an inconsistent effect on adherence” [56].

Thus, Big Data sets are useful to assess adherence in different profiles of drug users, analyse the factors related to adherence, explore causes of discontinuation and to compare results across different populations. With this information, drug users at the highest risk of non-adherence can be identified and tailored interventions can be designed and implemented. It is of paramount importance to consider that most of current interventions to address adherence are using, or are based on IT (Information Technology) solutions.

These, however, are not currently based on standardized measures of adherence [55]. Another potential technology approach for prediction and assessment of adherence is Artificial Intelligence (AI). With AI onboard, Big Data may be analysed both retrospectively, as well as in real time, allowing for more personalized healthcare. However, a major hindrance to the adoption of AI is, yet again, the lack of sound operational measures of adherence to properly train the algorithms.

Along with individual health, public health is sure to benefit from the introduction of standardised measures of adherence. Such measures will enable comparison of adherence rates within and across different countries, populations and disease groups, allowing for fair benchmarking of interventions, better planning and practical implementation. In fact, more and more often, medication adherence is accepted as a measure of the quality of care provided by physicians as well as the quality and effectiveness of the entire healthcare system [55, 57]. Also in this area, lack of standardised measures causes the problem of non-adherence to be often overlooked in national agendas. In fact, only a few countries systematically monitor adherence. Therefore, the recent OECD report calls for standardization in order to allow for international benchmarking [55].

Recent outbreak of COVID-19 pandemic proved the extraordinary role that infoepidemiology (i.e. information epidemiology) can play in the management of major public health problems [58]. Let this lesson be the inspiration for wider adoption of digitization in healthcare, in general, and faster utilization of the potential of Big Data for the management of adherence, in particular.

Conclusions

Ongoing digitization of the healthcare sector, and availability of Big Data repositories create unprecedented opportunity to study patient adherence at a mass scale, both retrospectively and in real time. Obvious benefits that could be derived for science, as well as for individual and public health, are hindered by the current lack of standards of adherence-related data analysis. What sort of standards need to be agreed to change this scenario? Firstly, there needs to be a standard format for the data collected in Big Data databases – such as EHRs, as well as prescribing and dispensing registers – to allow for smooth and effective assessment of adherence parameters. Secondly, sound metrics need to be developed to

process this raw data. Thirdly, standards of presentation of adherence measures being assessed within Big Data need to be agreed.

Bearing in mind the troublesome history of healthcare sector digitization, this plan may appear to be ambitious. However, the authors of this publication are motivated to face the challenge and develop these highly needed global standards, discuss them with the scientific world and finally, agree a common consensus. Therefore, everybody interested is invited to join our efforts within the new initiative that we want to call DIGI.PASs - introducing Patient Adherence Standard measures to be used with Big Data collections available in the DIGItal repositories.

References

1. Sabate, E (ed.). Adherence to long-term therapies evidence for action. World Health Organization, Geneva, 2003. ISBN 9241545992.

2. Cutler RL, Fernandez-Llimos F, Frommer M et al. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018;8(1):e016982. PMID: 29358417.

3. Walsh CA, Cahir C, Tecklenborg S et al. The association between medication non-adherence and adverse health outcomes in ageing populations: A systematic review and meta-analysis. Br J Clin Pharmacol. 2019 Nov;85(11):2464-2478. doi: 10.1111/bcp.14075. PMID: 31486099.

4. European Commission. Eurostat News. he EU's population projected up to 2100. https://ec.europa.eu/eurostat/web/products-eurostat-news/-/DDN-20190710-1 [Last accessed: April 13, 2020.]

5. Wong MC, Liu J, Zhou S et al. The association between multimorbidity and poor adherence with cardiovascular medications. Int J Cardiol. 2014 Dec 15;177(2):477-82. PMID: 25443249.

6. Nieuwlaat R, Wilczynski N, Navarro T, at al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014 Nov 20;(11):CD000011. doi: 10.1002/14651858.CD000011.pub4. PMID: 25412402.

7. Car J, Tan WS, Huang Z, Sloot P, Franklin BD. eHealth in the future of medications management: personalisation, monitoring and adherence. BMC Med. 2017 Apr 5;15(1):73. PMID: 28376771.

8. Linn AJ, Vervloet M, van Dijk L et al. Effects of eHealth interventions on medication adherence: a systematic review of the literature. J Med Internet Res. 2011 Dec 5;13(4):e103. doi: 10.2196/jmir.1738. PMID: 22138112.

9. Bailey SC, Wallia A, Wright S et al. Electronic Health Record-Based Strategy to Promote Medication Adherence Among Patients With Diabetes: Longitudinal Observational Study. J Med Internet Res. 2019 Oct 21;21(10):e13499. doi: 10.2196/13499. PMID: 31638592.

10. Hamine S, Gerth-Guyette E, Faulx D et al. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: a systematic review. J Med Internet Res. 2015 Feb 24;17(2):e52. doi: 10.2196/jmir.3951. PubMed PMID: 25803266.

11. Pérez-Jover V, Sala-González M, Guilabert M, Mira JJ. Mobile Apps for Increasing Treatment Adherence: Systematic Review. J Med Internet Res. 2019 Jun 18;21(6):e12505. doi: 10.2196/12505. PMID: 31215517.

12. Priority Recommendations of the HMA-EMA joint Big Data Task Force. Available at: https://www.ema.europa.eu/en/documents/other/priority-recommendations-hma-ema-joint-big-data-task-force_en.pdf Last accessed: April 13, 2020.

13. European Commission. eHealth: Digital health and care. https://ec.europa.eu/health/ehealth/overview_en [Last accessed: April 13, 2020]

14. https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-data-strategy Last accessed: April 13, 2020.

15. Aznar-Lou I, Fernández A, Gil-Girbau M et al. Initial medication non-adherence: prevalence and predictive factors in a cohort of 1.6 million primary care patients. Br J Clin Pharmacol. 2017 Jun;83(6):1328-1340. PMID: 28229476.

16. Kardas P, Cieszyński J, Czech M et al. Primary nonadherence to medication and its drivers in Poland: findings from the electronic prescription pilot analysis. Pol Arch Intern Med. 2020 Jan 31;130(1):8-16. doi: 10.20452/pamw.14994. PMID: 31559971.

17. Laius O, Pisarev H, Volmer D et al. Adherence to osteoporosis medicines in Estonia-a comprehensive 15-year retrospective prescriptions database study. Arch Osteoporos. 2017 Dec;12(1):59. PMID: 28643266.

18. Dima A, Allemann S, Dediu D. AdhereR: An Open Science Approach to Estimating Adherence to Medications Using Electronic Healthcare Databases. Stud Health Technol Inform. 2019 Aug 21;264:1451-1452. PMID: 31438176.

19. OECD (2019), Health in the 21st Century: Putting Data to Work for Stronger Health Systems, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/e3b23f8e-en. ISBN 978-92-64-59753-2.

20. Auffray C, Balling R, Barroso I, et al. Making sense of big data in health research: Towards an EU action plan. Genome Med. 2016;8(1):71. PMID: 27338147

21. https://www.hl7.org/implement/standards/product_brief.cfm?product_id=7V [Last accessed: April 13, 2020.]
22. https://www.hl7.org/fhir/ [Last accessed: April 13, 2020.]
23. https://www.iso.org/standard/67868.html [Last accessed: April 13, 2020.]
24. https://www.iso.org/standard/57757.html [Last accessed: April 13, 2020.]

25. Kruse CS, Goswamy R, Raval Y, Marawi S. Challenges and Opportunities of Big Data in Health Care: A Systematic Review. JMIR Med Inform. 2016;4(4):e38. PMID: 27872036

26. Ngiam KY, Khor IW. Big data and machine learning algorithms for health-care delivery. Lancet Oncol. 2019;20(5):e262-e273. PMID: 31162085

27. Shortreed SM, Cook AJ, Coley RY, Bobb JF, Nelson JC. Challenges and Opportunities for Using Big Health Care Data to Advance Medical Science and Public Health. Am J Epidemiol. 2019;188(5):851-861. PMID: 30877288

28. Vrijens B, De Geest S, Hughes DA et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012; 73(5): 691-705. PMID: 22486599

29. De Geest S, Zullig LL, Dunbar-Jacob J et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med. 2018 Jul 3;169(1):30-35. PubMed PMID: 29946690.

30. "Europe's contributions to ICT Standardisation globally - Impacts from StandICT.eu funding"(https://www.standict.eu/sites/default/files/Final%20Impact%20Report%20Europe%E2%80%99s%20contributions%20to%20ICT%20Standardisation%20globally%20-%20Impacts%20from%20StandICT.eu%20funding.pdf)

31. https://bioportal.bioontology.org/ontologies/ADHER_INTCARE_EN

32. Malo S, Aguilar-Palacio I, Feja C et al. Different approaches to the assessment of adherence and persistence with cardiovascular-disease preventive medications. Curr Med Res Opin. 2017 Jul;33(7):1329-1336. PMID: 28422521.

33. Lima-Dellamora EDC, Osorio-de-Castro CGS, Madruga LGDSL, Azeredo TB. Use of pharmacy records to measure treatment adherence: a critical review of the literature. Cad Saude Publica. 2017 Apr 20;33(3):e00136216. PMID: 28444026.

34. Franklin JM, Gopalakrishnan C, Krumme AA et al. The relative benefits of claims and

electronic health record data for predicting medication adherence trajectory. Am Heart J. 2018 Mar;197:153-162. PMID: 29447776.

35. Zullig LL, Curtis LH. A population health perspective on a claims and electronic health record-based tool to screen for suboptimal medication adherence. Am Heart J. 2018 Mar;197:150-152. PMID: 29447775.

36. Menditto E, Bolufer De Gea A et al. Scaling up health knowledge at European level requires sharing integrated data: an approach for collection of database specification. Clinicoecon Outcomes Res. 2016 Jun 13;8:253-65. PubMed PMID: 27358570.

37. Menditto E, Cahir C, Aza-Pascual-Salcedo M et al. Adherence to chronic medication in older populations: application of a common protocol among three European cohorts. Patient Prefer Adherence. 2018;12:1975-1987. PubMed PMID: 30323567.

38. Hutchins DS, Zeber JE, Roberts CS et al. Initial Medication Adherence-Review and Recommendations for Good Practices in Outcomes Research: An ISPOR Medication Adherence and Persistence Special Interest Group Report. Value Health. 2015 Jul;18(5):690-9. PMID: 26297098.

39. Peterson AM, Nau DP, Cramer JA et al. A checklist for medication compliance and persistence studies using retrospective databases. Value Health. 2007 Jan-Feb;10(1):3-12. PMID: 17261111.

40. Arnet I, Kooij MJ, Messerli M et al. Proposal of Standardization to Assess Adherence With Medication Records: Methodology Matters. Ann Pharmacother. 2016 May;50(5):360-8. PMID: 26917817.

41. Raebel MA, Schmittdiel J, Karter AJ et al. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. Med Care. 2013; 51(8 Suppl 3): S11-S21. PMID: 23774515.

42. Lehmann A, Aslani P, Ahmed R et al. Assessing medication adherence: options to consider. Int J Clin Pharm. 2014; 36(1): 55-69. PMID: 24166659.

43. Williams AB, Amico KR, Bova C et al. A proposal for quality standards for measuring medication adherence in research. AIDS Behav. 2013; 17(1): 284-97. PMID: 22407465.

44. Sattler EL, Lee JS, Perri M 3rd. Medication (re)fill adherence measures derived from pharmacy claims data in older Americans: a review of the literature. Drugs Aging. 2013 Jun;30(6):383-99. PMID: 23553512.

45. U.S. Centers for Medicare & Medicaid Services. Quality Measures. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityMeasures/index?redirect=/qualitymeasures/ [Last accessed: April 13, 2020.]

46. Parekh N, Munshi KD, Hernandez I et al. Impact of Star Rating Medication Adherence Measures on Adherence for Targeted and Nontargeted Medications. Value Health. 2019 Nov;22(11):1266-1274. PMID: 31708063.

47. Kim S, Bennett K, Wallace E et al. Measuring medication adherence in older community-dwelling patients with multimorbidity. Eur J Clin Pharmacol. 2018 Mar;74(3):357-364. doi: 10.1007/s00228-017-2388. PMID: 29199370.

48. Arnet I, Greenland M, Knuiman MW et al. Operationalization and validation of a novel method to calculate adherence to polypharmacy with refill data from the Australian pharmaceutical benefits scheme (PBS) database. Clin Epidemiol. 2018 Sep 6;10:1181-1194. PMID: 30233252.

49. Moreno Juste A, Gimeno Miguel A, Poblador Plou B et al. Adherence to treatment of hypertension, hypercholesterolaemia and diabetes in an elderly population of a Spanish cohort. Med Clin (Barc). 2019 Jul 5;153(1):1-5. PMID: 30503066.

50. Alfian SD, Pradipta IS, Hak E et al. A systematic review finds inconsistency in the measures used to estimate adherence and persistence to multiple cardiometabolic medications. J Clin Epidemiol. 2019 Apr;108:44-53. PubMed PMID: 30537541.

51. Pednekar PP, Ágh T, Malmenäs M et al. Methods for Measuring Multiple Medication Adherence: A Systematic Review-Report of the ISPOR Medication Adherence and Persistence Special Interest Group. Value Health. 2019 Feb;22(2):139-156. PMID: 30711058.

52. Dima AL, Dediu D. Computation of adherence to medication and visualization of medication histories in R with AdhereR: Towards transparent and reproducible use of electronic healthcare data. PLoS One. 2017 Apr 26;12(4):e0174426. PMID: 28445530.

53. Román-Villarán E, Pérez-Leon FP, Escobar-Rodriguez GA et al. EIP on AHA Ontology for adherence: Knowledge representation advanced tools. Transl Med UniSa. 2019 Jan 6;19:49-53. PubMed PMID: 31360667.

54. Baumgartner PC, Haynes RB, Hersberger KE et al. A Systematic Review of Medication Adherence Thresholds Dependent of Clinical Outcomes. Front Pharmacol. 2018 Nov 20;9:1290. doi: 10.3389/fphar.2018.01290. PMID: 30524276.

55. Khan R, Socha-Dietrich K. Investing in medication adherence improves health outcomes and health system efficiency: Adherence to medicines for diabetes, hypertension, and hyperlipidaemia. 2018. OECD Health Working Papers No. 105. https://dx.doi.org/10.1787/8178962c-en ISSN: 18152015.

56. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front. Pharmacol. 2013; 4:91. doi: 10.3389/fphar.2013.00091. PMID: 23898295

57. Seabury SA, Dougherty JS, Sullivan J. Medication adherence as a measure of the quality of care provided by physicians. Am J Manag Care. 2019 Feb;25(2):78-83. PMID: 30763038.

58. Mavragani A. Tracking COVID-19 in Europe: Infodemiology Approach. JMIR Public Health Surveill. 2020 Apr 20;6(2):e18941. doi: 10.2196/18941. PMID: 32250957.

Supplementary Files