PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Developing a medication adherence technologies repository: proposed structure and protocol for an online real-time Delphi study
AUTHORS	Nabergoj Makovec , Urska; Goetzinger, Catherine; Ribaut, Janette; Barnestein-Fonseca, Pilar; Haupenthal, Frederik; Herdeiro, Maria; Grant, Sean; Jácome, Cristina; Marques Roque, Fatima; Smits, Dins; Tadic, Ivana; Dima, Alexandra; ENABLE, Collaborators

VERSION 1 – REVIEW

REVIEWER	Patel, Tejal University of Waterloo
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	This is a well written and comprehensive protocol for the development and validation of the attributes of a repository of medication adherence technologies. The authors should be commended for their thoroughness in laying the foundational context for such a repository. I have a few comments for consideration. 1. Abstract a. The introduction in the abstract is not clear that the repository being discussed is intended for medication adherence technologies. Additionally, could you elaborate on the needs of the diverse stakeholders that you are intending to meet in the introduction? For example, will this repository enable a patient to identify a medication adherence technology to improve medication adherence based on the ABC and WHO definitions or to improve certain health outcomes? 2. Methods and Analysis a. Dates of the Delphi RT are not included. Please indicate when the Delphi consensus process will be initiated and your anticipated date for final analysis b. Clarify why other technologies that focus on other medication management goals are being excluded from the repository. Would not all technologies that support medication management or medication self-management improve adherence to medications, especially among those individuals who are un-intentionally non-adherent? c. Clarify where intentional non-adherence would be captured in your attribute groups? d. Clarify how will patient/caregiver participants be identified and invited? Please clarify how one measures 30 years of experience

	as a patient. What kind of expertise/professional experience will they be reporting? e. Please explain your sample size. It appears you are inviting at least 195 panellists but will stop the survey when you meet 3 criteria, one of which (and the one that requires the largest sample) is at least a 30% response rate. Assuming a minimum sample of 195 invited panellists, a 30% response rate will be achieved with 60 persons. Although you have established other criteria to ensure a representative sample in terms of panellists from each stakeholder group and countries, are you not intending to ensure representative samples from different ages, genders, years of experience, etc? f. Finally, please detail your strategy for ensuring that you will have adequate responses for each survey question. Your survey is quite lengthy and may induce survey fatigue for participants, with the potential for a declining number of responses for questions later in the survey. You have operationalized survey completion as completion of 75% of the repository questions. How have you strategized ensuring the last 25% of the questions on the survey have adequate number of responses to analyze? 3. Supplementary Material a. The supplementary material provided is unwieldy with many blank pages, tables that are cut-off and poor organization. It is quite frustrating to review. I encourage the authors to improve the submission of the supplementary material.

REVIEWER	Khan, Faiz Xi'an Jiaotong University, Department of Pharmacy Administration and Clinical Pharmacy School of Pharmacy, Health Science Center
REVIEW RETURNED	10-Jan-2022

GENERAL COMMENTS	The study protocols entitled “Developing a medication adherence technologies repository: proposed structure and protocol for an online real-time Delphi study” have highlighted the important aspects of medication adherence technologies and repositories. The following are my comments for the Authors. 1. The title needs to modify, and little changes would be appreciated like adding “study protocol” in the title. 2. Mention the abbreviation for “ENABLE”. 3. The three domains will be covered and at the same time how would it be possible to cover all the aspects and objectives of the study? 4. Overall, how the 39 countries and ENABLE members will engage in the study and execution, and what were the selection criteria for the 9 countries selection? 5. Where are the adherence stands beside the repository in the objectives or reflection to it unable to understand as so many things are proposed to be going on at the same time? 6. The sampling technique is needed to be more clarified and the recruitment of the members would be on a randomization basis or not? 7. The main evidence which has been drawn from the present protocol is not cleared. Very specific evidence must be mentioned that must represent the whole picture of the protocol. Such measuring scales and other factors must be controlled and the conclusion and the evidence from the proposed study must be cleared that would be helpful for the readers and researchers in the field.

	8. A short Discussion part needs to be mentioned of the protocols, to measure the expected outcomes of the proposed study with already published literature. Wish you all the best. Thanks, and Best Regards.,

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dr. Tejal Patel, University of Waterloo
Comments to the Author:
This is a well written and comprehensive protocol for the development and validation of the attributes of a repository of medication adherence technologies. The authors should be commended for their thoroughness in laying the foundational context for such a repository. I have a few comments for consideration.

R: Thank you for your feedback and evaluation. We addressed your comments in the following text.

1. Abstract
a. The introduction in the abstract is not clear that the repository being discussed is intended for medication adherence technologies. Additionally, could you elaborate on the needs of the diverse stakeholders that you are intending to meet in the introduction? For example, will this repository enable a patient to identify a medication adherence technology to improve medication adherence based on the ABC and WHO definitions or to improve certain health outcomes?

R: Thank you for rising this issue. For clarification we added medication adherence technologies in the introduction of the abstract. The sentence now reads:
“An online interactive repository of available medication adherence technologies may facilitate their selection and adoption by different stakeholders.”

We agree on the value of elaborating more on the diversity of the stakeholder needs, as it is an important reason to develop this structure. As the abstract has a limited word count allowed, we have elaborated on the rationale and diverse stakeholders needs in the manuscript. Table 2 contains the rationale for inclusion of certain attribute groups with description of reasons and specific needs and distinctions between stakeholders. The topic is also covered in the introduction section, which we tried to make more distinct with some additions (in bold):
“Therefore, ENABLE sets out to develop and maintain a public online repository of MATech where patients, HCPs, researchers, and healthcare managers would be able to access and select technologies for adoption in their adherence management activities. For example, a patient may be interested more in the practical benefits of using a MATech in their daily lives, while a researcher may be keen to examine in detail the methodology theory and evidence base behind the MATech development. To meet this goal, the ENABLE repository would need to represent a flexible knowledge management system that would include information relevant to the needs of different stakeholders in a user-friendly format.”

Finally, assessing the more specific needs of the stakeholders will also be part of the next steps in the repository development.

2. Methods and Analysis
a. Dates of the Delphi RT are not included. Please indicate when the Delphi consensus process will be initiated and your anticipated date for final analysis

R: We added the planned dates in the Methods, Data collection section, lines 337-338, which now read:
"The survey will be conducted from 1st October 2021 to 15th January 2022 in three stages: …"

The anticipated date for final analysis was added, in Methods, Final repository structure section, lines 445-446, which now read:
"After conducting the analyses described above (planned to be finalized at the end of April 2022), results suggesting modifications to the proposed structure will be considered for adoption by the Steering Committee in a subsequent version…"

b. Clarify why other technologies that focus on other medication management goals are being excluded from the repository. Would not all technologies that support medication management or medication self-management improve adherence to medications, especially among those individuals who are un-intentionally non-adherent?

R: We agree that there are several technologies/solutions that can influence medication adherence, either directly or indirectly. We address this topic in the introduction section, where we describe how different fields influence medication adherence and how one needs to be aware of all the different approaches/needs when developing a repository and when deciding what to include in it.

The choice of focusing on technologies that are more directly linked to medication adherence (and thus exclude other medication management goals) was an informed choice made by the steering committee based on the different considerations also keeping in mind the feasibility of the development process. The objectives and the scope of the repository are set by the Action's Memorandum of Understanding, that narrows the scope of the Action to technologies directly linked to medication adherence. However, we expect the repository to be a living resource and we hope that it will continue to grow beyond this narrow initial scope to include other medication management technologies indirectly related to adherence.

We believe the clarification for the scope is described in the introduction section, where the background and rationale for the Delphi study is explained in detail.

"Digital technologies have increasingly gained interest as new interventions for supporting medication adherence have been developed. A diversity of technologies has been proposed, from electronic monitoring devices to mobile applications, to support medication adherence measurements and empower patients with their disease management. However, the rapidly expanding offer of medication adherence technologies (MATech) makes it increasingly difficult to access, evaluate, and compare different technologies to make informed decisions and select appropriate tools for specific clinical or research needs...."

"The ENABLE COST Action ('European Network to Advance Best practices & technoLogy on medication adherencE', CA19132)[8] was initiated by experts in medication adherence and digital technologies to fill these gaps regarding evidence and implementation of MATech within healthcare systems. ENABLE aims to raise awareness of available technologies, expand multidisciplinary knowledge on medication adherence at multiple levels, accelerate knowledge translation to clinical practice, and collaborate towards economically viable implementation of best practices and technologies across European healthcare systems. These objectives are being pursued within a 4-

year period (2020-2023), by three distinct and interrelated working groups (WGs) that map best practices available (WG1), identify and showcase adherence technologies (WG2), and identify suitable reimbursement strategies for implementation in healthcare systems (WG3), supported transversally by a WG4 coordinating communication and dissemination…"

"The field of medication adherence is highly interdisciplinary, therefore a useful repository would cross multiple knowledge domains and align with several standards, whether medical (e.g., World Health Organisation International Classification of Disease; WHO ICD[18]), behavioural (e.g., the Behaviour Change Intervention Ontology; BCIO19 [20]), or technical (e.g., WHO Classification of Digital Health Interventions; WHO DHIs[21])."

c. Clarify where intentional non-adherence would be captured in your attribute groups?

R: In our view, intentional and non-intentional nonadherence are broad categories that represent a simplified version of adherence determinants. In many behavioural models, intention is intermediary to behaviour and is determined by a range of determinants, that we have described here using the COM-B model. The advantage of using this model is that it has corresponding behaviour change techniques that can be used to precisely describe the content of MATech, as adherence interventions. Thus, we prefer to consider it as included in the definition of several other attributes and their labels under D2.4.2. Type of adherence management; D2.4.2.B. Support/intervention especially the attribute groups behaviour determinants (D2.4.2.B.2) and behaviour change techniques (D2.4.2.B.3).

These attribute groups, its labels and definitions are well described in Table 2 and in the Supplementary Excel file.

d. Clarify how will patient/caregiver participants be identified and invited? Please clarify how one measures 30 years of experience as a patient. What kind of expertise/professional experience will they be reporting?

R: The sampling technique is the same for all stakeholders, patient representatives are included as described in the section Sampling and sample size (lines 304-326).

The main source of panellists were ENABLE country representatives, which were invited to provide contacts from 1-2 patient representatives from their country. Patients that can be active members of a patient association, patient advocates in different institutions, participants of related research projects, or patients from health institutions. We have modified the text of this section to make it clearer for the reader (lines 308-309 and 313-316)

"…(iii) patient representation (age > 18 years, active representative in patient associations or health care facilities), …"

and

"Purposive sampling will be applied to identify potential panellists. First, requests will be sent through the ENABLE Cost Action membership list to representatives of all 39 countries, requesting them to identify suitable panellists from all five backgrounds. ENABLE members will provide the steering committee the name, background, and e-mail for every potential panellist."

The RT Delphi we aimed to conduct was not specifically asking for expertise in the field of medication adherence or technologies. The RT Delphi focused on gathering distinct perspectives (patient

perspective among them) on relevant, clear and complete repository content to meet their needs. Therefore, we aimed to capture participants' own perceptions about their own experiences, personal or professional; a person who has been living with a chronic condition for 5 years can perceive themselves to have 5 years' experience with managing the condition in their daily lives. In addition, we asked for this specific participant's characteristic to help us describe the sample and understand/interpret the answers and comments we will receive during the study. Hence, the experience was not a criterion to be able to participate, but more a characteristic that describes the diversity of the sample. We have added the following clarification in the section Data collection (lines 370-371):

"This information will also be used to examine differences in participants' ratings and comments depending on their background and location."

e. Please explain your sample size. It appears you are inviting at least 195 panellists but will stop the survey when you meet 3 criteria, one of which (and the one that requires the largest sample) is at least a 30% response rate. Assuming a minimum sample of 195 invited panellists, a 30% response rate will be achieved with 60 persons. Although you have established other criteria to ensure a representative sample in terms of panellists from each stakeholder group and countries, are you not intending to ensure representative samples from different ages, genders, years of experience, etc?

R: We considered that more focus should be put on representativeness of the stakeholder groups and geographical spread, which reflects different experiences and needs for the repository and the diversity of the ENABLE Action. This focus is reflected in the stopping criteria for data collection (lines 375-382) and thus covers the largest sample. We have not set specific criteria to aim for representativeness in different ages, genders and years of experience. These characteristics were meant more as sample descriptive characteristics. Regardless, we have monitored invitations and responses of the participants during the study and can report a good distribution among these characteristics. We added the following clarification to distinguish between stakeholder group and location vs other characteristics (line 368-371):

"For sample description purposes, participants will be requested to provide information on their expertise (profession, years of experience, relevant professional experiences) and demographic characteristics (age, gender, country of practice). This information will also be used to examine differences in participants' ratings and comments depending on their background and location."

f. Finally, please detail your strategy for ensuring that you will have adequate responses for each survey question. Your survey is quite lengthy and may induce survey fatigue for participants, with the potential for a declining number of responses for questions later in the survey. You have operationalized survey completion as completion of 75% of the repository questions. How have you strategized ensuring the last 25% of the questions on the survey have adequate number of responses to analyse?

R: We planned to moderate (and also closely moderated) the Delphi process as explained in section Data collection, lines 359-366. We acknowledge, the survey was lengthy, which can present a barrier to persist until the end. Therefore, we monitored the debate in the forum under each question. If a technical issue occurred, we responded directly to it by providing a solution. We sent weekly reminders to participants, and we also prepared weekly bulletins within the platform, where we outlined the study progress and certain most commented issues to encourage further participation. We have added a clarification after the enumeration of the monitoring strategies, as follows (lines 359-366):

“We will moderate the discussion in the following ways: (i) address technical issues with the platform by responding to the comment when the issues will be solved or provide instructions how to manage the issue and (ii) outline the progress of the study and the most commented questions in bulletins send through the platform once a week. We considered these strategies to encourage panellists to participate, taking into account the length of the survey and the complexity of the concepts they are rating. “

To reduce complexity (and thus participation burden), we selected the same type/format for all questions so that participants are able to get familiar with it and continue completing the survey. Moreover, we used similar wording and phrasing in the questions as much as possible, to make it easier to continue responding. This is shown in the outline of the Delphi survey (Supplementary material).
As mentioned previously, we monitored the response during the study. We observed that people either dropped out after the first question (after carefully reading the requirements of the study, which they have also received beforehand); or completed it, which suggests that the choices we made regarding the format and wording were helpful to reduce participation burden.

3. Supplementary Material
a. The supplementary material provided is unwieldy with many blank pages, tables that are cut-off and poor organization. It is quite frustrating to review. I encourage the authors to improve the submission of the supplementary material.

R: We are sorry for the inconvenience, unfortunately the documents got compressed into one PDF file during the submission process and the formatting was lost. The supplementary materials we provided are divided in several documents. The file with several cut offs and blank pages is originally an Excel file including details of the attributes, labels and definitions in several sheets, each for one attribute group. If you would like to examine the supplementary files in more detail, the editor may be able to provide the originals.

Reviewer 2
Dr. Faiz Khan, Xi'an Jiaotong University, Quaid-i-Azam University Comments to the Author:
The study protocols entitled “Developing a medication adherence technologies repository: proposed structure and protocol for an online real-time Delphi study” have highlighted the important aspects of medication adherence technologies and repositories. The following are my comments for the Authors.

R: Thank you for your feedback and evaluation. We addressed your comments in the following text.

1. The title needs to modify, and little changes would be appreciated like adding “study protocol” in the title.

R: The title includes the word protocol and specifies the study design (online real time Delphi study), We consider it is easier to read in this format, as we need to also mention the development of the structure in the title as an important part of our methodology:

“Developing a medication adherence technologies repository: proposed structure and protocol for an online real-time Delphi study”

1. Mention the abbreviation for “ENABLE”.

R: The abbreviation for ENABLE is included in the Introduction, see line 141-142. We bolded the capital letters in the Action title to make it more clear for the reader.

“The ENABLE COST Action (‘European Network to Advance Best practices & technoLogy on medication adherencE’, CA19132) …”

1. The three domains will be covered and at the same time how would it be possible to cover all the aspects and objectives of the study?

R: The survey outline is provided in the supplementary material (please see the Survey outline document), which shows that we were able to cover all three domains and attribute groups in the survey. Certain attributes were grouped into groups of attributes to simplify and shorten the survey as much as possible. We acknowledge the survey is/was quite lengthy, however the participants were aware of this beforehand (in the invitation to participate and once again before starting the survey). In the revised manuscript we emphasized what strategies we used to encourage panellists to actively participate and persist regardless of the study length (lines 359-366):

“We will moderate the discussion in the following ways: (i) address technical issues with the platform by responding to the comment when the issues will be solved or provide instructions how to manage the issue and (ii) outline the progress of the study and the most commented questions in bulletins send through the platform once a week. We considered these strategies to encourage panellists to participate, taking into account the length of the survey and the complexity of the concepts they are rating. “

1. Overall, how the 39 countries and ENABLE members will engage in the study and execution, and what were the selection criteria for the 9 countries selection?

R: All 39 countries are included in the ENABLE COST Action (the project). All 39 countries participating to the ENABLE COST Action (project) were contacted and invited to participated to the RT-Delphi survey. There was no selection of countries. We tried to make this even clearer in the revised text in the section Sampling and sample size, lines 305-306, line 310-311 and lines 313-315:

“We aim to include stakeholders from all 39 countries, participating in the COST ENABLE, covering 5 different backgrounds per country:”

“Hence, the targeted sample size is at least 195 panellists to be invited in the study (39 countries * 5 stakeholders).”

“Purposive sampling will be applied to identify potential panellists. First, requests will be sent through the ENABLE Cost Action membership list to representatives of all 39 countries, requesting them to identify suitable panellists from all five backgrounds.”

1. Where are the adherence stands beside the repository in the objectives or reflection to it unable to understand as so many things are proposed to be going on at the same time?

R: The introduction section explains the background and rationale for the study and all aspects where medication adherence is addressed. To make it clearer what the manuscript entail we modified the rationale and aim at the end of the Introduction section, lines 183-191

“Considering these quality standards and following methodological recommendations,22-24 the initial version of the repository structure was prepared. A stakeholder consultation process is proposed to explore their views and level of agreement on the relevance, clarity and completeness of the initial version.22 23 The resulting improved version would represent the structure of the ENABLE repository, which will be tested and populated in subsequent steps with users and developers of available technologies.
The proposed manuscript covers two elements:
1) Description of the proposed structure for the repository
2) Protocol of the RT Delphi study, which we used to explore stakeholder feedback on the proposed structure.”

The adherence descriptors are covered in Domain 2 of the structure. All attribute groups starting with D2 encompass specific adherence elements. In the Delphi survey, this domain (D2) is covered by eleven questions (see Supplementary - Summary of the Delphi survey page 4-10). All questions that start with D2 are included in this domain. Regardless, medication adherence is the core element of the whole repository (ENABLE Action), and it is hence emphasized in all attributes, labels and definitions.

1. The sampling technique is needed to be more clarified and the recruitment of the members would be on a randomization basis or not?

R: To clarify, this is a protocol for a Real-Time Delphi study, which does not require randomization. RT thus stands for real-time, not randomised trial. To make sure no misunderstandings occur, we have spelled out the abbreviation RT as ‘real time’ in all occurrences in the manuscript. We left the abbreviation RT-Delphi as is, given it is an established term:

“We will perform an online real-time Delphi (RT-Delphi) survey to explore the level of agreement on the MATech definition and relevance, clarity and completeness of the proposed framework of attributes defining the repository structure and gain a deeper insight into stakeholders’ distinct needs and requirements. “

We asked the ENABLE country representatives to provide contacts from their countries. For each country at least one person, for each stakeholder group – one researcher, one practitioner, one decision maker, one patient representative and one technology developer. If we did not have a response from the countries, we tried to contact key international organisations listed, to provide us with contacts to be able to reach the sample size. We tried to make it clearer, also in response to reviewer 1, in the section Sampling and sample size (lines 313-316 and lines 323-326):

“First, requests will be sent through the ENABLE Cost Action membership list to representatives of all countries, requesting them to identify suitable panellists with all backgrounds. ENABLE members will provide the steering committee the name, background, and e-mail for every potential panellist."

“To reach simple size and variation in sample characteristics, key international organizations from the field (e.g., ESPACOMP, PCNE, ESCP, WONCA, EMA, EPF, EARTO, EuroDURG etc.) will be contacted to fill any missing gaps, if needed.”

1. The main evidence which has been drawn from the present protocol is not cleared. Very specific evidence must be mentioned that must represent the whole picture of the protocol. Such measuring scales and other factors must be controlled and the conclusion and the evidence from the proposed study must be cleared that would be helpful for the readers and researchers in the field.

R: We agree it is important to specify the outcomes clearly. As this is a Delphi study, the typical aim in healthcare research is to consult different stakeholders on the matters proposed and to (if possible) reach consensus (e.g., definition, structure, core elements,). Hence, in our Real Time-Delphi we had two outcomes: relevance and clarity. We measured how relevant a certain attribute group is and how clear we defined it in the developing part. These two outcomes were measured with the use of 9-point Likert scale and responses will be evaluated with the use of RAND/UCLA Appropriateness Method (RAM). More about the Delphi studies and RAM method can be found here: https://www.rand.org/health-care/surveys_tools/appropriateness.html

In addition, we left open text fields for participants to provide comments on the proposed structure and its completeness. In this case content analysis (a qualitative approach) will be used to evaluate panellists' comments.

We have explained our outcome in the Methods sections

- Lines 353-358 – we explain how we define relevance and clarity and how we measure it.
- Lines 358-359 – we explain the open text field and the reasons to use them
- Data analysis, lines 390-409 – we detail how the RAM method will be applied in the analysis of the results
- Data analysis, lines 410-412 – we detail how we will analyse the open text boxes (panellists' comments).
- We further detail also subgroup analysis (per stakeholder groups), where the intraclass correlation will be used as a measure (lines 413-424)
- Finally, we will evaluate the stability of responses with the coefficient of quartile variation, which is a process indicator in Delphi studies (lines 425-443)

Through the whole manuscript, we also extensively referenced scientific publications on all used methodology and provided arguments why certain choices are suggested.

1. A short Discussion part needs to be mentioned of the protocols, to measure the expected outcomes of the proposed study with already published literature.

R: We considered your suggestion and added a section titled Future implications and challenges, where we address expected next steps and what challenges we might encounter on the road to repository development (lines 467-480):

"Future implications and challenges

The proposed scope and framework of attributes together with findings from this Delphi study will represent the first steps on the pathway to create an evidence-based, interoperable and user-friendly MATech repository. Following the Delphi consultation and integration of the repository module on the ENABLE website[87], providers of MATech (public or private) would be invited to upload information on their products via a MATech description form based on the final repository structure. The accuracy of the information would be verified by an independent review panel through a procedure yet to be established. Important challenges lay ahead, such as how to select MATech for inclusion in the repository given the broad scope of the definitions proposed, how to ensure accurate information about the technologies included, how to provide the information in other languages than English and in non-technical language accessible for all, and how to maintain a representative and varied offer of technologies in the long term. Nevertheless, the ENABLE repository promises to bring together stakeholders from different backgrounds to build a common language which can have an important positive impact on medication adherence research and practice."

To clarify further, BMJ Authors instructions guided us to prepare the protocol in a way, where interpretation, arguments for methodological choices and comparison with existing literature are included under each section. For example:

1. The choice of study design is provided together with arguments for the choice, and we extensively referenced it there. Please see section Choice and description of the study design, lines 280-302.
2. The development of the repository structure is also extensively referenced as to where the elements, we considered/included, come from and what has been already published on the topic. Table 2 consists of a rationale why we included certain attribute groups and where did the state of the art come from (see Table 2).

Therefore, by using this approach, the expected outcomes and comparison with the existing literature is already embedded in the main text of the proposed protocol.

VERSION 2 – REVIEW

REVIEWER	Patel, Tejal University of Waterloo
REVIEW RETURNED	24-Mar-2022

GENERAL COMMENTS	Thank you for answering my questions. No further comments.

REVIEWER	Khan, Faiz Xi'an Jiaotong University, Department of Pharmacy Administration and Clinical Pharmacy School of Pharmacy, Health Science Center
REVIEW RETURNED	14-Mar-2022

GENERAL COMMENTS	Current state of the protocols have been improved. The authors have replied and addressed all my comments. So, with immense pleasure the paper may be accepted.