



WP2 / WP6 – Core Outcome Set Project

DELPHI - Core Outcome Set (COS) definition in

Chronic lymphocytic leukemia (CLL)

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A. INTRODUCTION

The HARMONY Alliance is a public-private European Network established in 2017, which currently includes 53 partners and 27 associated members from 22 countries. One of HARMONY's goals is to use Big Data to improve understanding and treatment of hematological malignancies (HM) (1). In order to achieve this aim, HARMONY is structured into eight work packages of which work package 2 (WP2) is focused on defining outcomes sets for seven HMs and one outcome set applicable for all HMs. In accordance, this study will be performed to define the core outcome set (COS) in chronic lymphocytic leukemia (CLL), one out of seven hematological malignancies predefined in HARMONY.

Chronic lymphocytic leukemia is the most common leukemia in western countries. CLL is characterized by clonal proliferation and accumulation of mature b-cells within the blood, bone marrow, lymph nodes and spleen (2). Recently new recommendations of the international workshop on CLL (iwCLL) were published with clearly defined criteria for diagnosis of CLL (3). The diagnosis of CLL requires the presence of a defined count of monoclonal B-lymphocytes in the peripheral blood, confirmed by flow cytometry.

There are two widely accepted, longstanding clinical staging system, Rai (4) and Binet (5). Both systems classify in prognostic subgroups based on simple clinical and laboratory tests. In recent years CLL therapy made strong progress and a new prognostic score was needed. The CLL International Prognostic Index (CLL-IPI) is based on five independent prognostic factors and clearly shows prognostic subgroups and can also identify patients without need of therapy (6).

Currently, several randomized controlled clinical trials examine appropriate therapy protocols as well as new innovative compounds with the objective to improve both CLL patient outcomes and patient management. Also, few groups gave recommendations for patient-reported factors and health-related outcomes in patients with CLL (7,8). But generally valid recommendations of outcomes that should be measured are still missing.

Unfortunately, the ability to compare clinical trials is limited due to differences in their measured outcomes. This lack of standardization relates to the current lack of a core outcomes set (COS) that can be utilized to guide outcomes selection and harmonization in CLL in current and future trials. For example, measurement of long-term side effects and their influence on the patients' quality of life has not yet been assessed in most of these clinical trials.

A COS is a minimum set of outcomes developed by consensus, and a minimum set of outcomes is a reference point and provides the minimum outcomes that should be collected in further clinical trials on a given condition. It is common to develop a COS by consensus by using multi-stakeholder consensus-based Delphi methodology. Use of a COS improves the comparability of clinical trials or other research in real world settings, improves consistency of reporting, reduces selective reporting bias and ensures that appropriate outcomes valued by a range of stakeholders are measured. COS can be incorporated into clinical guidelines and improve the clinical practice and patient outcomes and management.

In this context, a clear distinction between outcomes and prognostic factors is crucial. An outcome is defined as an effect of treatment or intervention on the disease or well-being of patients. On the other hand, prognostic factors can be understood as a patient characteristic that identifies subgroups of patients that are likely to have different outcomes. As such prognostic factors are not part of a



core outcome set and will not be included within this study. Since some patient characteristics, e.g. age or cytogenetics are relevant for treatment decisions and patient prognosis, these variables should be still collected in every future trial.

To define a COS “what to measure” should first be identified. After that, “how the outcome should be defined and measured” can be determined (9).

Key stakeholders who are dedicated to provide their expert feedback are selected based on their skills and experience relevant to the disease or project. The stakeholders include health service users, health service practitioners, researchers, regulators, drug developer, patients and patient advocates. Participants of all stakeholder groups were in particular recruited from members of the HARMONY work packages 2 and 6, but also participants outside the HARMONY Alliance are welcome to take part of the Delphi survey within their stakeholder group.

In order to ensure that the defined COS is acceptable for each stakeholder group it is important to include as many stakeholders’ groups as possible in particular patients and patient advocates. To increase the influence of patient groups for the definition of outcomes an additional category is included in the analysis of the Delphi survey, called patient important. This category will be used in the final analysis to mark a specific outcome as patient important. It is recommended to discuss these specific outcomes separately in the final consensus meeting.

B. PROJECT GOALS

Based on this background, this project aims to define a COS for CLL agreed by consensus of all stakeholder groups and to define standardized outcomes to be measured in future clinical trials and observational studies throughout Europe.

The protocol has been written following the COS-STAP recommendations (10).

C. METHODS

The development of the COS will follow COMET recommendations from the international COS-STAD study (10, 11).

The Delphi method will be used to achieve a consensus from different stakeholder groups. Recruitment of participants mainly takes place from members of the HARMONY Alliance, as described above. The Delphi instrument used is an online tool, DelphiManager, provided by the COMET Initiative (12).



Participants

1. Patients

In this Delphi survey patients equal or older than 18 years with CLL can participate. Different subtypes of CLL are equally included, regardless of previous treatments including stem cell transplantation. Patients treated as outpatients were included as well as patients treated in hospital settings. Due to the use of English for the Delphi survey, participation is limited to patients understanding English.

2. Clinicians and Clinical researcher

Every clinician within or outside the HARMONY Alliance with experiences in CLL can take part in the survey.

3. Drug developers

Participants have been recruited from stakeholder organizations that are members of HARMONY, including European Federation of Pharmaceutical Industries and Associations (EFPIA) member companies.

4. Regulators

Recruitment of participants will be performed within the HARMONY Alliance with support of Workpackage 6 and 7.

Data protection

The personal data of the participants (name, home country and email address) will be stored only for the duration of the survey on a secure server provided by the DelphiManager. After completion of the survey all data will be deleted.

By registering, all participants provide consent to the terms of the Delphi survey and they agree to the use of their data in the way described in the survey protocol.

Study management group

A study management group has been assembled as recommended by COMET (9) to oversee the project. Members include a study coordinator, a hematologist with leading roles in CLL treatment and clinical trials, drug developer with experience in past and current trials, patient advocates, and methodological experts with experiences of systematic reviews and Delphi studies.



Selection of the outcome list for CLL

The empirical basis for identifying a long list of preliminary set of CLL outcomes for the Delphi study so far has been threefold:

First – A literature research was conducted in the COMET database to get an overview of the outcomes already used in existing clinical trials (13-16). The primary outcomes list was generated by extracting outcomes from the published literature and the views of clinicians and trialists (13-16).

Second – several semi-structured interviews of clinical public and private key opinion leaders were conducted to assess the initial selection of the particular outcome parameters and additional outcomes were supplemented (14).

Third – in order to include the patients' perspective, we consulted with patient representatives, people who have or have had MM, to complement the preliminary list of outcomes by including additional outcomes and revise the list in accordance with their comments. In addition a specific literature research for patient-reported outcomes in CLL-patients was performed and included in the preliminary list (13-16).

D. DELPHI PROCESS

The preliminary CLL outcome list ([Annex 1](#)), which was created in this threefold process mentioned above, will be used in the Delphi survey in a representative pool of stakeholders to agree in a pre-defined and iterative process on a COS for CLL.

To date, there is no recommendation found in literature regarding the number of participants to include in a Delphi survey. For certain stakeholder groups, for example for regulators it may be hard to recruit a large number of participants, which may lead to an imbalance of group size. With providing summarized results for each stakeholder group separately, the effect of inequitable distribution of group size is minimized.

The Delphi will be performed in at least three sequential rounds. In every round, the stakeholders will be asked to rate the importance of each outcome based on their personal experiences. Each outcome will be ranked into three categories (1-3 “not important”, 4-6 “important but not critical” and 7-9 “critical”) using a Likert scale of 1 to 9. After the completion of the first round of the Delphi survey no new participant will be invited.

Within the questionnaire, outcomes will be grouped into domains so that similar or related outcomes can be viewed and rated together. Each outcome will be described both in plain language. Plain language descriptions are used from lists provided by COMET (12, 17, 18) and also from native-speakers with medical background.



The language used in the Delphi survey is English. Before the first iteration, each participant is asked to which stakeholder group, he/she belongs. Once the individual participant has completed the first ranking round, he/she will also be able to provide additional feedback, by suggesting additional outcome parameters, which might be added within the subsequent Delphi rounds. This additional outcome will be added to the following Delphi rounds when two or more participants proposed this outcome to be included.

After each round, all participants will be provided with their own answers and an anonymized, graphical summary of the other participants' answers across all different stakeholder groups, in terms of the percentage scoring each of 1 to 9 on a particular outcome. Thereby feedback is provided from all stakeholder groups separately.

This allows the participants to revise their answers during the next round of the Delphi survey by taking the previous round's results into account. No outcome will be dropped out between the first two rounds, so the participants can revise their initial ranking. The range of answers should decrease from round to round and a consensus opinion result, a core outcome set is defined. The process is stopped after pre-defined consensus criteria as described below.

After the final round a face-to-face consensus meeting will take place to finally discuss the results and to reaffirm the defined COS.

It will be important that as many participants as possible complete every round of the Delphi survey to ensure robust results of high representativeness.

The rate of non-response after the Delphi rounds, so called attrition is often highly variable. The attrition rate described over different Delphi studies varies from 0% to 20%. There is no recommendation regarding attrition rates, however an acceptable response rate would be 80%. To increase the response rates personalized email reminders will be sent out.

Attrition bias may occur if participants give no response to subsequent rounds of survey.

Little evidence is available regarding the extent to which attrition bias influences the Delphi result. To examine the attrition bias the average scores after round 2 will be compared for those completing the next round and those dropping out after round 2.

E. RESULTS AND ANALYSIS

To reduce potential bias in the interpretation of the results a clear definition of consensus is important. Consensus can be considered to have been reached if the majority of participants rank an outcome in a similar way. There are three categories of consensus defined in previous works (17), that will be modified used after the final Delphi round to assign each outcome to a category for each stakeholder group:



1. Consensus in

50 % or more respondents over all the respondents (clinicians, EFPIA members, regulators/HTA, patients and patient advocates) scored the outcome as critically important (7-9) AND 15% or fewer rate the outcome as limited important (1-3)

2. Consensus out

50 % or more of all the respondents (clinicians, EFPIA members, regulators/HTA, patients and patient advocates) scored the outcome as limited important (1-3) AND 15 % or fewer rate the outcome as critically important (7-9)

3. No consensus

Outcomes that do not achieve a consensus through the several rounds in the Delphi survey will be discussed at a consensus meeting to finally ratify the CLL core outcome set. This applies especially for outcomes that are necessary for special stakeholder groups and have not reached consensus in accordance with the consensus criteria. It is planned to do a separate explanatory analysis for outcomes which are considered as important for the patients.

After completing the last Delphi round, each participant will be asked about willingness to participate in a face-to-face consensus meeting. The participants to this meeting will be randomly selected from this Delphi's participants, who completed the whole Delphi process. In addition, representatives from all stakeholder groups will be part of this meeting.

The analysis of the Delphi study described in this protocol will use descriptive statistics. The results for each of the Delphi rounds, for each outcome and for each stakeholder group, will be presented in frequency tables. Quantitative analysis of the Delphi survey include calculations of i) percentage of panel's response rates and ii) percentages of responses in each of the three importance categories (1-3: "not important", 4-6: "important but not critical" and 7-9: "critical" based on 9-point Likert scale) for each outcome. (22,23)

The data will be also displayed graphically, e.g. using histograms, for each stakeholder group and for each outcome. The plots will be reproduced for each round to further visualize the stability of panel's opinion.

The analysis of the Delphi study will be performed using the R statistical software version 3.5.2 (24). As mentioned above the exploratory analysis of the outcomes considered as important for patients will be analyzed as following: The median Likert score for the patient group at the end of each round will be calculated and those outcomes achieving a median of greater or equal to 7 (≥ 7) will be considered as important to patients.



F. STRENGTH & LIMITATIONS

As mentioned above different stakeholder groups take part in the Delphi survey. To ensure the impact of the highly important patient involvement in this process, a further specific category was added, called patient important. Thereby outcomes with a special interest for patients can be marked and emphasized in analysis.

The language used in the Delphi survey is English. This limits the group of people to participate in the Delphi to persons who do speak English. This might introduce a bias with regard to the countries participating in the Delphi, with e.g. a potential overrepresentation of English speaking countries. While it was considered to translate the questionnaires into other European languages, this could pose additional problems and might introduce a different bias, e.g. depending on quality of the translations or depending on the number of participants per language, to name only few.

Finally, a potential unequal distribution in group size as discussed above is likely, but by presenting summarized results for each stakeholder group separately, this potential source of bias can be addressed, as described by COMET.

G. OUTLOOK

The anticipated way of developing the COS ensures that clinicians, industry, health authorities, as well as patients are involved in each stage of the development. In addition, the Delphi survey helps to make sure, that the COS represents the priorities of all stakeholders. Ultimately, utilization of the COS will improve the relevance of trial endpoints to all stakeholders. Furthermore, it will increase the capacity for data synthesis between different trials.

In parallel to the completion of the Delphi survey in CLL, it is intended to start Delphi surveys to define a COS for the remaining hematological malignancies included in HARMONY.

Finally, based on the results of the COS definition for the hematological malignancies included in HARMONY a standardized COS applicable for all HMs will be established/created.



ANNEX 1 | PRELIMINARY OUTCOME LIST FOR MM

Name	HelpText	DomainName
Pain	When your body hurts, including aching joints, which may vary in intensity from mild discomfort to pain that limits activities of daily life, limits self care and/or requires medication or hospitalisation. Medication may be necessary	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Diarrhea	Passing looser stools (poo) or passing stools more often than is normal for you	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Constipation	Having difficulty passing stools (poo), which may be small and hard	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Nausea	Feeling or being sick, which may lead to impact on intake of food and/or fluids and/or normal activities	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Changes in taste and smell	Loss of the senses of smell and taste, including the reduced ability to smell or taste, for instance, sweet, sour, bitter or salty	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical



Anorexia	Loss of appetite, which may lead to weight loss and malnutrition	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Fatigue	Extreme or persistent tiredness that's not related to recent activity	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Shortness of breath (Dyspnoea)	Shortness of breath or breathing problems, which may happen at rest and may limit activities of daily living or self care, and may require treatment	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Change in sexual function	Such as changes in sexual desire, sexual dysfunction, erectile dysfunction, difficulties reaching orgasm, vaginal dryness in women, other genital changes that lead to pain during sexual activity, difficulty feeling arousal and pleasure during sex	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Infertility	Inability to get pregnant or to produce healthy sperms	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Hair loss	Alopecia or baldness, loss of hair from part of the head or body	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Sleep changes	Finding it difficult to get to sleep or to stay asleep	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical



Anxiety	Feelings of constant worry, or deep concern or uneasy about uncertainties	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Depression	Feelings of severe sadness and unhappiness, often with decreased energy, constant feelings of guilt, doubt or self-blame, worthlessness and hopelessness	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Psychosocial function	Problems with mental processes of perception, memory, judgment, reasoning or thinking with an effect on relationships with partner, family and friends including ability to join in with social activities	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical
Physical function	The effect of CLL or its treatment on day to day physical activities; for example, walking, climbing stairs, driving	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - other concerns
Role function	The effect of CLL or its treatment on your role; for example, ability to look after children or to work or earn money	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - other concerns
Financial concerns	Financial losses because of co-payment for medical treatment, and if a patient was working before disease diagnosis or progression, loss of salary during sick leave, which may include leave taken by a carer	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - other concerns
Eating and drinking	The effect of CLL or its treatment on eating and drinking	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - other concerns



Cost of CLL treatment	Money which must be spend on CLL treatment	Use of Health care resources
Emergency Unit admissions	Emergency or unplanned hospital treatment is necessary	Use of Health care resources
Intensive care admissions	Treatment on an intensive care ward due to serious or life threatening disease progression or side-effects	Use of Health care resources
Outpatient visits	Treatment or diagnostic visits in hospital without spending a night there	Use of Health care resources
Need of caregiver assistance	Requirement for assistance given by caregiver (who could be a family member, friend or a professional care giver) in or outside the hospital	Use of Health care resources
Complete Response - CR (complete remission)	CLL gets better, resulting in no residual lymphoma in bone marrow and normal peripher blood cells	Medical concerns - type of event
Response - Stable disease (SD)	CLL stays the same after treatment. It is not getting better or worse	Medical concerns - type of event



Response - Progressive disease (PD)	CLL getting worse after treatment	Medical concerns - type of event
Relapse - Clinical relapse	Symptomatic return of CLL after a patient initially responds well to treatment	Medical concerns - type of event
Relapse - biochemical relapse	Symptomatic return of CLL after a patient initially responds well to treatment	Medical concerns - type of event
Relapse - molecular relapse	Symptomatic return of CLL after a patient initially responds well to treatment	Medical concerns - type of event
Cause of death	Death for any reason, whether related to CLL or not. This records the specific reason for death, not the time until death	Medical concerns - type of event
Overall survival (OS)	Length of time that a patient remains alive from either the date of diagnosis or the start of treatment for the CLL	Medical concerns - Time to event
Progression free survival (PFS)	Time until someone's CLL either gets worse or they die from any cause	Medical concerns - Time to event



Event free survival (EFS)	Time until someone's CLL either gets worse, they die from any cause or they stop their treatment because of side-effects	Medical concerns - Time to event
Duration of response (DOR)	Time from a positive response to a treatment to when the CLL starts to recur / to get worse	Medical concerns - Time to event
Time to progression (TTP)	Time until someone's CLL recurs / gets worse (excluding death)	Medical concerns - Time to event
Time to response (TTR)	Time from starting a treatment until a positive response to treatment	Medical concerns - Time to event
Time to treatment (TTT)	Time until first treatment is necessary	Medical concerns - Time to event
Time to next treatment (TTNT)	Time after first treatment and the next treatment is necessary	Medical concerns - Time to event
Treatment free intervall (TFI)	Time from the end of the treatment until the next therapy is needed	Medical concerns - Time to event



Time to transformation	Time until CLL transforms in a high-risk lymphoma or leukemia	Medical concerns - Time to event
Infections	How often and how bad a patient gets sick or picks up a bacterial, viral or fungal infection, that needs antibacterial or antifungal treatment. Number of bacterial, viral or fungal infections, that needs antibacterial or antifungal treatment	Medical concerns - clinical parameter
transfusion independence	No need for regular transfusions of red blood cells or thrombocytes	Medical concerns - clinical parameter
Reduction of systemic symptoms	Treatment response, that reduces symptoms	Medical concerns - clinical parameter
Minimal residual disease (MRD) molecular / on cell-basis	The level of CLL that can be detected as measured by using a DNA sequencing technique	Medical results - minimal residual disease
Minimal residual disease (MRD) flow cytometry	The level of CLL that can be detected as measured by using a special technique	Medical results - minimal residual disease
Minimal residual disease (MRD) imaging / radiology	The level of CLL that can be detected as measured by using a imaging method	Medical results - minimal residual disease



AEs (adverse events) and SAEs (serious adverse event)	A negative event or side-effect that happens during or after treatment, a clinical decision classified according to the latest "Common Terminology Criteria for Adverse Events", a list of adverse events. For each adverse event there is a grading for severity	Safety concerns - adverse events / harmful events
Medication adherence	Patients take their medication as prescribed by the doctor	Safety concerns - adverse events / harmful events
Discontinuation of treatment	Patient decides to stop treatment themselves or under the direction of his/her doctor for any reason other than finishing a course of treatment	Safety concerns - adverse events / harmful events
Hematological toxicity	Side-effects that cause changes in the blood or number of blood cells (e.g. low red blood count, low white blood count, low platelets, among others)	Safety concerns - adverse events / harmful events
Non-Hematological toxicity	Side-effects that cause changes anywhere other than in the blood, e.g. nausea, neuropathy, mucositis, renal or liver failure, infections	Safety concerns - adverse events / harmful events
Tolerability related outcomes	Measurement of how well patients are able to manage side-effects and whether they need to reduce dose or stop treatment as a result	Safety concerns - adverse events / harmful events
Second primary malignancies (SPM)	A new cancer occurring in someone who has had a cancer in the past. It is different to recurrence, which is where the original cancer has returned	Safety concerns - adverse events / harmful events



ANNEX 2 | REFERENCES

- (1) <https://www.harmony-alliance.eu>
- (2) Rozman C, et al., Chronic lymphocytic leukemia. *N Engl. J Med.* 1995. 333. 1052-1057
- (3) Hallek M, et al., iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018. 131. 2745-2760
- (4) Rai KR, et al., Clinical staging of chronic lymphocytic leukemia. *Blood* 1975. 46. 219-234
- (5) Binet JL, et al., A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer.* 1981. 48. 198-204.
- (6) International CLL IPI working group. An international prognostic index for patients with chronic lymphocytic leukemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol.* 2016. 17. 779-790.
- (7) Efficace F, et al., Health-related quality of life assessment and reported outcomes in leukemia randomized controlled trials – A systematic review to evaluate the added value in supporting clinical decision making. *European Journal of Cancer.* 2008. 44. 1497 - 1506
- (8) Cannella L, et al., Health-related quality of life and symptom assessment in randomized trials of patients with leukemia and myelodysplastic syndromes: What have we learned? *Critical reviews in Oncology/Hematology.* 2015. 96. 542-554.
- (9) Williamson PR, et al., The COMET Handbook: version 1.0. *Trials*, 2017. **18**(Suppl 3): p. 280
- (10) Kirkham JJ et al., Core Outcome Set-STANDARDISED Protocol Items: The COS-STAP Statement. *Trials.* 2019. **20**: 116
- (11) Kirkham JJ, et al., Core Outcome Set-STANDARDS for Development: The COS-STAD recommendations. *PLoS Med.* 2017. **14**(11): p. e1002447
- (12) COMET database - <http://www.comet-initiative.org>
- (13) <http://www.comet-initiative.org> -accessed 27th May 2019
- (14) Werner S, Schulze-Rath R Assessment of outcomes for hematological malignancies included in the COMET database 2017 (unpublished)
- (15) Werner S, Schukze-Rath R Results of semi-structured telephone interviews on outcome definition with members of WP2 2018
- (16) Efficace F, et al., Patient-reported outcomes in hematology: it is time to focus more on them in clinical trials and hematology practice? *Blood.* 2017. **130**(7): 859-66
- (17) Fish R, et al., Core outcome research measures in anal cancer (CORMAC): protocol for systematic review, qualitative interviews and Delphi survey to develop a core outcome set in anal cancer. *BMJ Open.* 2017. **7**: p. e018726
- (18) Dictionary of outcome definitions – kindly provided by S. R. Dodd
- (19) Gargon E, et al., Choosing important health outcomes for comparative effectiveness research: a systematic review. *PLoS One*, 2014. **9**(6): p. e99111



- (20) Gorst SL, et al., Choosing important Health Outcomes for Comparative Effectiveness Research: An Updated Review and User Survey. PLoS One, 2016. **11**(1): p. e0146444
- (21) Gorst SL, et al., Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and Identification of Gaps. PLoS One, 2016. **11**(12): p. e0168403
- (22) Holey, Elizabeth A., et al. "An exploration of the use of simple statistics to measure consensus and stability in Delphi studies." *BMC medical research methodology* 7.1 (2007): 52.
- (23) Greatorex, J., & Dexter, T. (2000). An accessible analytical approach for investigating what happens between the rounds of a Delphi study. *Journal of advanced nursing*, 32(4), 1016-1024.
- (24) R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.



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