WP2 / WP6 – Core Outcome Set Project

DELPHI - Core Outcome Set (COS) definition in

Chronic Myeloid Leukemia (CML)

1 December, 2021

INDEX

A. INTRODUCTION

The HARMONY Alliance is a public-private European Network established in 2017, which includes 53 partners and 43 associated members from 17 countries, including 9 pharmaceutical companies and 9 Patient Umbrella Organizations. One of HARMONY's objectives is to use Big Data to improve understanding and treatment of hematological malignancies (HM) (1). HARMONY Plus is a new public-private partnership within the HARMONY Alliance, launched at 6 October 2020. One of Harmony Plus objectives is to expand the scope of the HARMONY Alliance to cover remaining HM not included in the HARMONY project (2). Just like the previous HARMONY project one work package within HARMONY Plus is focused on defining outcomes sets for further 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 Myeloid Leukemia (CML), one out of four hematological malignancies predefined in HARMONY Plus.

CML is a clonal bone marrow stem cell disorder, with an increased and unregulated growth of myeloid cells in the bone marrow. CML appears more commonly in elderly adults. Diagnosis is based on cytogenetic and molecular analyses of blood cells. CML is characterized by a balanced genetic translocation, t(9;22)(q34;q11.2), involving a fusion of the Abelson gene (ABL1) from chromosome 9q34 with the breakpoint cluster region (BCR) gene on chromosome 22q11.2. This rearrangement is known as the Philadelphia chromosome. The molecular consequence of this translocation is the generation of a BCR-ABL1 fusion oncogene, which in turn translates into a BCR-ABL1 oncoprotein (3). These findings form the basis for first-line treatment – using tyrosin-kinase inhibitors (TKIs) (4). After normal survival has been achieved in most patients with chronic myeloid leukemia (CML), a new goal for treating CML is survival at good quality of life, with treatment discontinuation in sustained deep molecular response (DMR; MR^4 or deeper) and treatment-free remission (TFR) (5-7). In addition to these new outcomes resulting from the therapy successes, more and more long-term outcomes on quality of life are coming into focus.

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 COS that can be utilized to guide outcomes selection and harmonization in CML 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 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.

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 developers, patients and patient advocates.

Participants of all stakeholder groups were in particular recruited from members of the HARMONY work packages, 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

The aim of this project is therefore to define a COS for CML 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 (8).

C. METHODS

The development of the COS will follow COMET recommendations from the international COS-STAD study (8,9).

To achieve consensus from different stakeholder groups the Delphi method will be used. The Delphi instrument used is an online tool, DelphiManager, provided by the COMET Initiative (10). A more detailed description of the methodology can be found in section D. Recruitment of participants mainly takes place from members of the HARMONY Alliance.

Participants

1. Patients

In this Delphi survey patients equal or older than 18 years with CML can participate. Different subtypes of CML are equally included, regardless of previous treatments including stem cell transplantation. Patients treated as outpatients are 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 researchers

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

3. Drug developers

Participants have been recruited from stakeholder organizations that are members of HARMONY Plus, 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 Work Package 6.

Data protection

The personal data of 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.

Selection of the outcome list for CML

The empirical basis for identifying a list of preliminary CML outcomes for the Delphi study so far has been threefold a two-step process:

First – A literature research was conducted in the COMET database to get an overview of the outcomes already used in existing clinical trials (11). The primary outcomes list was generated by extracting outcomes from the published literature (3-6).

Second – in order to include the patients' perspective, patient advocates and people who have or have had CML were invited 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 CML-patients was performed and included in the preliminary list (12).

D. DELPHI PROCESS

The preliminary CML outcome list created after the process described above (Annex 1), 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 CML.

The Delphi survey will include two rounds. In each 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.

Based on the experience of the previous harmony surveys, the surveys planned now will be held as a so-called "hackathon".
For this purpose, a virtual meeting will take place on at least two days - this is also due to the current pandemic situation.
At these meetings, the surveys will be conducted in parallel by all participants. A major advantage of this is that any questions that arise can be asked and answered directly and, if necessary, support can be offered.

Within the questionnaire, outcomes will be grouped into domains so similar or related outcomes can be viewed and rated together. Each outcome will be described in plain language. Plain language descriptions are used from lists provided by patient advocates and also from native speakers with medical background.

When registering, participants will be asked which stakeholder group he/she belongs to. 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 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, 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.

E. RESULTS AND ANALYSIS

To reduce potential bias in the interpretation of the results a clear definition of consensus is crucial. There are three categories of consensus:

1. **Consensus in**
   70 % 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**
   70 % 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.

After completing the last Delphi round, each participant will be asked about willingness to participate in a final meeting, 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.

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 the panel's opinion.

The analysis of the Delphi study will be performed using the R statistical software version 3.5.2. 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 a few.

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, as described by COMET (13).

G. OUTLOOK

The anticipated way of developing the COS ensures that clinicians, industry, health authorities, as well as patients and patient advocates 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 CML, it is intended to start Delphi surveys to define a COS for the remaining hematological malignancies included in HARMONY Plus.

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

ANNEX 1 | PRELIMINARY OUTCOME LIST FOR CML

Name	HelpText	DomainName	DomainName - simplified
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	patient reported outcomes - PRO
Diarrhea / Constipation	Passing looser stools (poo), passing stools more often than is normal for you or problems with passing stools	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical	patient reported outcomes - PRO
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	patient reported outcomes - PRO
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	patient reported outcomes - PRO
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	patient reported outcomes - PRO
Fatigue	Extreme or persistant tiredness that's not related to recent activity	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical	patient reported outcomes - PRO
Shortness of breath (Dyspnoea)	Shortness of breath or breathing problems, which may happen at rest and may limit activities of	Patient reported concerns/outcomes (PRO) / Health related Quality of	patient reported outcomes - PRO

	daily living or self care, and may require treatment	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	patient reported outcomes - PRO
Infertility	Inability to get pregnant or to produce healthy sperms	Patient reported concerns/outcomes (PRO) / Health related Quality of Life - general, non-medical	patient reported outcomes - PRO
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	patient reported outcomes - PRO
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	patient reported outcomes - PRO
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	patient reported outcomes - PRO
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	patient reported outcomes - PRO
Psychosocial function	Problems with mental processes of perception, memory, judgment, reasoning or thinking with an effect on relationships with partner, family and friends	Patient reported concerns/outcomes (PRO) / Health related Quality of	patient reported outcomes - PRO

	including ability to join in with social activities	Life - general, non-medical	
Physical function	The effect of CML 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	patient reported outcomes - PRO
Role function	The effect of CML 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	patient reported outcomes - PRO
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	patient reported outcomes - PRO
Cost of CML treatment	Money which must be spend on CML treatment	Use of Health care resources	Use of Health care resources
Emergency Unit admissions	Emergency or unplanned hospital treatment is necessary	Use of Health care resources	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	Use of Health care resources
Outpatient visits	Treatment or diagnostic visits in hospital without spending a night there	Use of Health care resources	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	Use of Health care resources

Complete Response - CR (complete remission)	CML gets better, resulting in no residual lymphoma in bone marrow and normal peripher blood cells	Medical concerns - type of event	type of event
Response - major molecular remission (MMR)	No residual BCR ABL is detectable, deep response	Medical concerns - type of event	type of event
Response - Stable disease (SD)	CML stays the same after treatment. It is not getting better or worse	Medical concerns - type of event	type of event
Response - Progessive disease (PD)	CML getting worse after treatment	Medical concerns - type of event	type of event
Relapse - Clinical relapse	Symptomatic return of CML after a patient initially responds well to treatment	Medical concerns - type of event	type of event
Relapse - biochemical relapse	Symptomatic return of CML after a patient initially responds well to treatment	Medical concerns - type of event	type of event
Relapse - molecular relapse	Symptomatic return of CML after a patient initially responds well to treatment	Medical concerns - type of event	type of event
Cause of death	Death for any reason, whether related to CML or not. This records the specific reason for death, not the time until death	Medical concerns - type of event	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 CML	Medical concerns - Time to event	time to event
Progression free survival (PFS)	Time until someone's CML either gets worse or they die from any cause	Medical concerns - Time to event	time to event
Event free survival (EFS)	Time until someone's CML either gets worse, they die from any cause or they stop their treatment because of side-effects	Medical concerns - Time to event	time to event
Duration of response (DOR)	Time from a positive response to a treatment to when the CML starts to recur / to get worse	Medical concerns - Time to event	time to event
Time to progression (TTP)	Time until someone's CML recurs / gets worse (excluding death)	Medical concerns - Time to event	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 event
Time to treatment (TTT)	Time until first treatment is necessary	Medical concerns - Time to event	time to event
Time to next treatment (TTNT)	Time after first treatment and the next treatment is necessary	Medical concerns - Time to event	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 event
Time to blast crisis	Time until CML transforms in a blast crisis	Medical concerns - Time to event	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	clinical parameter
transfusion independence	No need for regular transfusions of red blood cells or thrombocytes	Medical concerns - clinical parameter	clinical parameter
Reduction of systemic symptoms	Treatment response, that reduces symptoms	Medical concerns - clinical parameter	clinical parameter
Minimal residual disease (MRD) molecular / on cell-basis	The level of CML that can be detected as measured by using a DNA sequencing technique	Medical results - minimal residual disease	clinical parameter
Minimal residual disease (MRD) flow cytometry	The level of CML that can be detected as measured by using a special technique	Medical results - minimal residual disease	clinical parameter
Minimal residual disease (MRD) imaging / radiology	The level of CML that can be detected as measured by using a imaging method	Medical results - minimal residual disease	clinical parameter

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	safety concerns
Medication adherence	Patients take their medication as prescribed by the doctor	Safety concerns - adverse events / harmful events	safety concerns
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	safety concerns
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	safety concerns
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	safety concerns
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	safety concerns

ANNEX 2 | REFERENCES

(1) **https://www.harmony-alliance.eu**

(2) HARMONY PLUS - HARMONY Alliance (harmony-alliance.eu)

(3) Jabbour E, Kantarjian H: Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring Am J Hematol 2018. 93(3)

(4) Hochhaus A et al. European Leukemia Net 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020. 34

(5) Hehlmann R: The New ELN Recommendations for Treating CML. J Clin Med. 2020. 9(11)

(6) Hehlmann R. Chronic Myeloid Leukemia in 2020. Hemasphere 2020 4(5)

(7) Garcia-Horton A, Lipton JH. Treatment Outcomes in Chronic Myeloid Leukemia: Does One Size Fit all?. JNCCN 2020 18(10)

(8) Kirkham JJ et al. Core Outcome Set-STAndardised Protocol Items: the COS-STAP Statement. Trials 2019 20(116)

(9) Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, et al. (2017) Core Outcome Set-STAndards for Development: The COS-STAD recommendations. PLOS Medicine 14(11)

(10) COMET Initiative | Home (comet-initiative.org)

(11) Research COMET Initiative | Home (comet-initiative.org) on 31.12.2021

(12) De Marchi F et al. How could patient reported outcomes improve patient management in chronic myeloid leukemia? Expert Rev Hematol. 2017. 10(1)

(13) Williamson PR, et al., The COMET Handbook: version 1.0. Trials, 2017. 18 (Suppl 3): p. 280

The HARMONY Alliance is funded through the Innovative Medicines Initiative (IMI), Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. HARMONY has received funding from IMI 2 Joint Undertaking and is listed under grant agreement No. 116026. This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI supports collaborative research projects and builds networks of industrial and academic experts to boost pharmaceutical innovation in Europe.

www.harmony-alliance.eu

HARMONY Communications Office
European Hematology Associations (EHA), The Hague, The Netherlands
- communications@harmony-alliance.eu

HARMONY Coordination Office
Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain
- harmonyoffice@ibsal.es