# **Supplementary Information- Annex A**

## ***Framework Evaluation- Outcomes for AML***

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| **DomainName** | **Name** | **HelpText** |
| **Clinical outcome - Time to event** | OS (overall survival) | Length of time that a patient remains alive from either the date of diagnosis or the start of treatment for the leukemia. |
| PFS (progression free survival) | Time until someone’s leukemia either gets worse or they die from any cause. |
| EFS (event free survival) | Time until someone’s leukemia either gets worse, they die from any cause or they stop their treatment because of side-effects. |
| DOR (duration of response) | Length of time from responding positively to a treatment to the leukemia starting to recur / to get worse. |
| TTP (time to progression) | Time until someone’s leukemia recurs / gets worse (excluding death). |
| TTR (time to response) | Time from starting a treatment until a positive response to treatment is documented. |
| LFS (leukemia free survival) | Time from receiving a transplant to evidence of leukemia getting worse. |
| DSS (disease specific survival) | Time until someone dies from leukemia, but not from other causes. |
| RFS (relapse free survival) | Time from achieving a leukemia-free state, to treatment until leukemia recurs. |
| **Clinical outcome - Event type** | Response - CR (complete remission) | Leukemia gets better, resulting in no evidence of abnormally high levels of "blast cells" in the bone marrow. Also no signs of leukemia detectable outside the bone marrow, and levels of other blood cells return to normal. |
| Response - CRi (complete remission with incomplete hematologic recovery) | All criteria of CR are met other than return of levels of certain white blood cells (neutrophils and platelets) to normal range. |
| Response - CR and MRD negative (complete remission and MRD negative) | All criteria of CR are met, plus "residual disease" that can only be detected by very sensitive measures (PCR or flow cytometry) is undetectable within a specific range. |
| Response - PR (partial remission) | Leukemia gets better, with a substantial reduction of "blast cells" compared to levels before treatment, but not enough to qualify as CR. Also, levels of other blood cells return to normal. |
| Response - SD (stable disease) | Leukemia stays the same after treatment. |
| Morphologic leukemia-free state (MLFS) | All criteria of CR related to reduction of "blast cells" in the bone marrow are met and no leukemia is detectable outside the bone marrow. Recovery of bone marrow function or blood cell counts are not considered for this outcome measure. |
| Relapse - Clinical relapse | Symptomatic return of leukemia after a patient initially responds well to treatment. |
| Relapse - Biochemical relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a blood test that suggests that leukemia may be recurring. |
| Relapse - Molecular relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a "minimal residual leukemia" test that suggests that leukemia may be recurring. |
| Cause of death | Death for any reason, whether related to leukemia or not. This records the specific reason for death, not the time until death. |
| PD (progressive disease) | Worsening of a patient's leukemia defined by a set of specific criteria for their leukemia. |
| **Clinical outcome - clinical parameter** | WBC (white blood cells) | Number of cells of the immune system that are involved in fighting leukemia but may also grow out of control, causing leukemia at diagnosis. |
| 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. |
| Use of G-CSF | Treatment given to help a patient to make a certain type of white blood cell called a neutrophil that is sometimes reduced in number because of treatment given or the patient's leukemia. |
| Bleeding | Number of events recorded when a patient has an unexpected bleeding event, which may indicate a deficiency or issue with a certain type of blood cell, and may require transfusions or other interventions. |
| **Clinical outcome - MRD** | Marrow MRD negativity | No detection of leukemia using very sensitive techniques to analyze bone marrow blood samples. |
| MRD cytogenetic | The level of leukemia that can be detected as measured by looking at how many cells there are with certain changes in the chromsomes. |
| MRD molecular | The level of leukemia that can be detected as measured by using a DNA sequencing technique. |
| MRD negativity post consolidation therapy | No detection of leukemia using specific techniques after the end of "consolidation" therapy, ie the completion of standard leukemia therapy with subsequent bone marrow transplantation. |
| **Safety outcome - AE / Toxicity** | AEs (adverse events) according to CTCAE v 4.0 | A negative event or side-effect that happens during or after treatment, classified according to the latest "Common Terminology Criteria for Adverse Events", a descriptive terminology of adverse events. For each adverse event there is a grading for severity. |
| SAEs (serious adverse event) | A negative event that happens during or after treatment that is life-threatening or results in death, that requires hospitalisation or an extension of hospitalisation, that causes a birth defect or that needs treatment to prevent permanent damage. |
| 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. |
| Hematological toxicity | Side-effects that cause changes in the blood or number of blood cells. |
| Non-Hematological toxicity | Side-effects that cause changes anywhere other than in the blood, e.g. nausea, neuropathy, mucositis, renal or liver failure, infections. |
| SPM (second primary malignancies) | 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. |
| GVHD (graft versus host disease) | Side-effect that can happen after somebody gets a bone marrow or stem cell transplant from somebody else, when the immune cells from the donor attack the body of the person given the transplant. |
| 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. |
| **PRO / HR-QoL - general - non-clinical** | Fatigue | Feeling more lethargic and tired than normal. |
| Insomnia | Finding it difficult to get to sleep or to stay asleep. |
| Pain | Unpleasant physical sensation, 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. |
| Diarrhea / constipation | Passing looser stools (poo) or passing stools more often than is normal for you / Having difficulty passing stools (poo), which may be small and hard. |
| Nausea | Feeling or being sick, which may lead to impact on intake of food and/or fluids and/or normal activities. |
| Anxiety | Feelings of constant worry, or deep concern or uneasy about uncertainties. |
| Dyspnoea | Shortness of breath, which may happen at rest and may limit activities of daily living or self care, and may require treatment. |
| Anorexia | Loss of appetite, which may lead to weight loss and malnutrition. |
| Cognitive problems | Problems with mental processes of perception, memory, judgment and reasoning. |
| Depression | Feelings of severe sadness and unhappiness, often with decreased energy, constant feelings of guilt, doubt or self-blame, worthlessness and hopelessness. |
| Sensory neuropathy | Problems involving damage to the peripheral nerves (those that connect the limbs and organs to the central nervous sysem and control sensation, movement and coordination) or symptoms caused by those issues, including numbness, tingling or burning sensations, increased sensivity to touch, weakness or dysfunction especially of extremities. |
| **PRO / HR-QoL - PRO domains** | Psychological function | The effect of leukemia or its treatment on psychological function; for example thinking and feeling. |
| Physical function | The effect of leukemia or its treatment on day to day physical activities; for example, walking, climbing stairs, driving. |
| Social function | The effect of leukemia or its treatment on relationships with partner, family and friends including ability to join in with social activities. |
| Role function | The effect of leukemia or its treatment on your role; for example, ability to look after children or to work or earn money. |
| Finances | 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. |
| Eating and drinking | The effect of leukemia or its treatment on eating and drinking. |
| **Health resource utilization - resource use** | Hospitalization days | Total days you are in hospital specifically because of leukemia or side effects in addition to planed days in hospital for treatment. |
| cost of leukemia treatment | Money which must be spend on leukemia treatment. |
| Emergency Unit admissions | Emergency or unplanned hospital treatment is necessary. |
| Intensive care admissions | Requirement for treatment on an intensive care ward due to serious or life threatening disease progression or side-effects. |
| Outpatient visits | Treatment or diagnostic visits in hospital without spending a night there. |
| Need of care giver assistance | Requirement for assistance given by caregiver (who could be a family member, friend or a professional care giver) in or outside the hospital. |

## ***Framework Evaluation- Outcomes for CLL***

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| **DomainName** | **Name** | **HelpText** |
| **Clinical outcome-Time to event** | OS (overall survival) | Length of time that a patient remains alive from either the date of diagnosis or the start of treatment for the CLL |
| PFS (progression free survival) | Time until someone’s CLL either gets worse or they die from any cause |
| EFS (event free survival) | Time until someone’s CLL either gets worse, they die from any cause or they stop their treatment because of side-effects. |
| CIR (cumulative incidence of relapse) | Method of calculating the risk of recurring CLL in a specific time period. |
| DOR (duration of response) | Length of time from responding positively to a treatment to the CLL starting to recur / to get worse |
| TTP (time to progression) | Time until someone’s CLL recurs / gets worse (excluding death) |
| TTR (time to response) | Time from starting a treatment until a positive response to treatment is documented |
| TTT (Time to treatment) | Time until first treatment is necessary |
| Time to next treatment (TTNT) | Time after first treatment and the next treatment is necessary |
| Treatment free intervall (TFI) | Time from the end of the treatment until the next therapy is needed |
| Time to transformation | Time until CLL transforms in a high-risk lymphoma or leukemia |
| Infection free interval (IFI) | Time frame a patients lives between 2 bouts of infections (without hospitalisations, antibiotics, anti-fungal or ant-viral treatment) |
| DSS (disease specific survival) | Time until someone dies from CLL, but not from other causes. |
| RFS (relapse free survival) | Time until someone’s CLL either gets worse, they die from any cause or they stop their treatment because of side-effects |
| **Clinical outcome - Event type** | Response - CR (complete remission) | CLL gets better, resulting in no residual lymphoma in bone marrow and normal peripher blood cells |
| Response - PR (partial response) | CLL gets better, regenerated blood picture, 5 - 25% blasts in bone marrow, or blastcount reduced by 50% |
| Response - SD (stable disease) | CLL stays the same after treatment. It is not getting better or worse |
| Relapse - biochemical relapse | Symptomatic return of CLL after a patient initially responds well to treatment |
| Relapse - molecular relapse | Symptomatic return of CLL after a patient initially responds well to treatment |
| HI (Hematological Improvement) | Increase of hemoglobin, platelet or neutophil count |
| 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 |
| PD (progressive disease) | CLL getting worse after treatment |
| **Clinical outcome - Clinical parameter** | 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 |
| Use of Granulocyte colony-stimulating factor (G-CSF) or erythropoiesis-stimulating agents (ESAs) | Treatment given to help a patient to make a certain type of white blood cell called a neutrophil or red blood cells called erythrocytes that is sometimes reduced in number because of treatment given or the patient's CLL |
| transfusion independence | No need for regular transfusions of red blood cells or thrombocytes |
| Reduction of systemic symptoms | Treatment response, that reduces symptoms |
| Bleeding | Some patients might be more likely to have "bleeding" events such as bruising because of their CLL or their treatment, which this captures. |
| **Clinical outcome - MRD** | Minimal residual disease (MRD) molecular | The level of CLL that can be detected as measured by using a DNA sequencing technique |
| Minimal residual disease (MRD) flow cytometry | The level of CLL that can be detected as measured by using a special technique |
| Minimal residual disease (MRD) imaging | The level of CLL that can be detected as measured by using a imaging method |
| **Safety outcome - AE / Toxicity** | 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 descriptive terminology of adverse events. For each adverse event there is a grading for severity |
| 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 |
| Medication adherence | Patients take their medication as prescribed by the doctor |
| Hematological toxicity | Side-effects that cause changes in the blood or number of blood cells (e.g. anemia, leukopenia, thrombocytopenia, among others) |
| Non-Hematological toxicity | Side-effects that cause changes anywhere other than in the blood, e.g. nausea, neuropathy, mucositis, renal or liver failure, infections |
| SPM (second primary malignancies) | 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 |
| GVHD (graft versus host disease) | Side-effect that can happen after somebody gets a bone marrow or stem cell transplant from somebody else, when the immune cells from the donor attack the body of the person given the transplant. |
| 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 |
| **Risk profile - basic characteristics** | Age | Age is often captured to see if people are more likely to get a CLL at a certain age, or if people of a certain age do better or worse when treated. |
| Gender | Gender is often captured to see if men or women are more likely to get a CLL or if their response or survival is different. |
| Renal function | How well the kidneys are working. |
| Anemia (Hb) | Having fewer red blood cells than normal reducing the amount of oxygen that can be carried in the blood |
| Karnofsky index | A measure of "performance status", or how well patients are able to function - for example, ability to carry on normal activity and self-care, or level of disability |
| ECOG | A measure of "performance status", or how well patients are able to function - ranges from 0 (no symptoms) to 4 (bedbound) for patients that are alive, or 5 for patients that have died. |
| **Risk profile - disease characteristics** | Cytogenetics | Measurement of how normal or abnormal a patient's chromosomes are - the genetic code of humans is usually packed into 23 pairs of chromosomes, but there may be changes in cancer cells or in the cells of people that are likely to get cancer. |
| Molecular genetics | Analysis of a patient's genes to understand if there are any changes to the genetic code that might make a patient more likely to get a CLL, that might affect how their CLL progresses, or that might help doctors to understand how they will respond to treatment. |
| Tumor activity (LDH) | Lactate dehydrogenase (LDH) is made by normal cells in the body, but the level in the blood is higher in patients with leukemia. Testing LDH levels in the blood can therefore be used to help with the diagnosis of leukemia and to estimate how aggressive it is. |
| **PRO / HR-QoL - general - non-clinical** | Fatigue | Significant or persistant tiredness that's not proportional to recent activity |
| Insomnia | Finding it difficult to get to sleep or to stay asleep. |
| Pain | Unpleasant physical sensation, 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 |
| Diarrhea | Passing looser stools (poo) or passing stools more often than is normal for you |
| Constipation | Having difficulty passing stools (poo), which may be small and hard |
| Nausea | Feeling or being sick, which may lead to impact on intake of food and/or fluids and/or normal activities |
| Anxiety | Feelings of constant worry, or deep concern or uneasy about uncertainties |
| Shortness of breath (Dyspnoea) | Shortness of breath or respiratory problems, which may happen at rest and may limit activities of daily living or self care, and may require treatment |
| Anorexia | Loss of appetite, which may lead to weight loss and malnutrition |
| Cognitive problems | Problems with mental processes of perception, memory, judgment and reasoning |
| Depression | Feelings of severe sadness and unhappiness, often with decreased energy, constant feelings of guilt, doubt or self-blame, worthlessness and hopelessness |
| 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 |
| Infertility | Inability to get pregnant or to produce healthy sperms |
| Hair loss | Alopecia or baldness, loss of hair from part of the head or body |
| Sleep changes | Finding it difficult to get to sleep or to stay asleep |
| Ruptures of capillaries on the legs | due to the lower number of platelets |
| Blood transfusion dependence | transfusion of red blood cells and platelets |
| Stem cells transplantation and GVHD | treatment |
| Increased appreciation of Life | positive change of attitudese towards life in general |
| Good QOL interval (GQI) | Time frame a patient is experiencing good adequate QOL (according to their subjective interpretation using PRO's or answers from QOL tools) |
| Changes in taste and smell | Loss of the senses of smell and taste, including the reduced ability to smell or taste specific substances, for instance, sweet, sour, bitter or salty |
| Sensory neuropathy | Problems involving damage to the peripheral nerves or symptoms of those issues, just like numbness, tingling or burning sensations, increased sensivity to touch, weakness or dysfunction especially of extremities, treatment-associated |
| **PRO / HR-QoL - PRO domains** | 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 |
| Physical function | The effect of CLL or its treatment on day to day physical activities; for example, walking, climbing stairs, driving |
| Social function | The effect of CLL or its treatment on relationships with partner, family and friends including ability to join in with social activities. |
| 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 |
| Financial toxicity | 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 |
| Holidays and travelling | The effect of CLL or its treatment on travelling and active leisure time |
| Eating and drinking | The effect of CLL or its treatment on eating and drinking |
| Work-life / studies | The effect of CLL or its treatment on working or studying |
| Effect on IADL (instrumental activity of daily life) | The effect of CLL or its treatment on the competence in the instrumental daily living, e.g. shopping, cooking, manage your finances |
| Effect on ADL (activities of daily life) | The effect of CLL or ist treatment on the competence in the daily living, e.g. washing, eating |
| **Health resource utilization - resource use** | Hospitalization days | additional days you are in hospital because of CLL or side effects |
| Cost of CLL treatment | Money which must be spend on CLL treatment |
| Emergency Unit admissions | Emergency or unplanned hospital treatment is necessary |
| Intensive care admissions | Requirement for treatment on an intensive care ward due to serious or life threatening disease progression or side-effects |
| Outpatient visits | Treatment or diagnostic visits in hospital without spending a night there |
| Need of care giver assistance | Requirement for assistance given by caregiver (who could be a family member, friend or a professional care giver) in or outside the hospital |
| Independent living | Ability to live independently, without reliance on carers for daily routine tasks, self-care, trips to hospital or clinical staff house visits |
| Sick leave | time you cannot work or have active time because of CLL or ist treatment |

## ***Framework Evaluation- Outcomes for MDS***

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| **DomainName** | **Name** | **HelpText** |
| **Clinical outcome-Time to event** | OS (overall survival) | Length of time that a patient remains alive from either the date of diagnosis or the start of treatment for the MDS |
| PFS (progression free survival) | Time until someone’s MDS either gets worse or they die from any cause |
| EFS (event free survival) | Time until someone’s MDS either gets worse, they die from any cause or they stop their treatment because of side-effects. |
| CIR (cumulative incidence of relapse) | Method of calculating the risk of recurring MDS in a specific time period. |
| DOR (duration of response) | Length of time from responding positively to a treatment to the MDS starting to recur / to get worse |
| TTP (time to progression) | Time until someone’s MDS recurs / gets worse (excluding death) |
| TTR (time to response) | Time from starting a treatment until a positive response to treatment is documented |
| TTT (Time to treatment) | Time until first treatment is necessary |
| Time to high-risk MDS | Time until low-risk MDS tranfsorms in a high-risk MDS |
| Time to AML | Time until MDS tranfsorms in a acute myeloid leukemia |
| LFS (leukemia free survival) | Time from receiving a transplant to evidence of leukemia getting worse. |
| Infection free interval (IFI) | Time frame a patients lives between 2 bouts of infections (without hospitalisations, antibiotics, anti-fungal or ant-viral treatment) |
| DSS (disease specific survival) | Time until someone dies from MDS, but not from other causes. |
| RFS (relapse free survival) | Time until someone’s MDS either gets worse, they die from any cause or they stop their treatment because of side-effects |
| **Clinical outcome-Event Type** | Response - CR (complete remission) | MDS gets better, resulting in no residual myeloblasts in bone marrow and normal peripher blood cells |
| Response - PR (partial response) | MDS gets better, regenerated blood picture, 5 - 25% blasts in bone marrow, or blastcount reduced by 50% |
| Response - SD (stable disease) | MDS stays the same after treatment. It is not getting better or worse |
| Relapse - Clinical relapse | Symptomatic return of MDS after a patient initially responds well to treatment |
| Biochemical relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a blood test that suggests that MDS may be recurring |
| Molecular relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a "minimal residual leukemia" test that suggests that leukemia may be recurring |
| HI (Hematological Improvement) | Increase of hemoglobin, platelet or neutophil count |
| Cause of death | Death for any reason, whether related to MDS or not. This records the specific reason for death, not the time until death |
| PD (progressive disease) | Worsening of a patient's MDS defined by a set of specific criteria for their MDS. |
| **Clinical outcome-Clinical parameter** | 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. |
| Use of Granulocyte colony-stimulating factor (G-CSF) or erythropoiesis-stimulating agents (ESAs) | Treatment given to help a patient to make a certain type of white blood cell called a neutrophil or red blood cells called erythrocytes that is sometimes reduced in number because of treatment given or the patient's MDS |
| transfusion independence | No need for regular transfusions of red blood cells or thrombocytes |
| Bleeding | Some patients might be more likely to have "bleeding" events such as bruising because of their MDS or their treatment, which this captures. |
| **Clinical outcome-MRD** | Minimal residual disease (MRD) molecular | The level of MDS that can be detected as measured by using a DNA sequencing technique |
| **Safety outcome-AE / Toxicity** | 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 descriptive terminology of adverse events. For each adverse event there is a grading for severity |
| 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 |
| Medication adherence | Patients take their medication as prescribed by the doctor |
| Hematological toxicity | Side-effects that cause changes in the blood or number of blood cells (e.g. anemia, leukopenia, thrombocytopenia, among others) |
| Non-Hematological toxicity | Side-effects that cause changes anywhere other than in the blood, e.g. nausea, neuropathy, mucositis, renal or liver failure, infections |
| SPM (second primary malignancies) | 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 |
| GVHD (graft versus host disease) | Side-effect that can happen after somebody gets a bone marrow or stem cell transplant from somebody else, when the immune cells from the donor attack the body of the person given the transplant. |
| 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 |
| **Risk profile - Basic characteristics** | Age | Age is often captured to see if people are more likely to get a MDS at a certain age, or if people of a certain age do better or worse when treated. |
| Gender | Gender is often captured to see if men or women are more likely to get a MDS or if their response or survival is different. |
| Renal function | How well the kidneys are working. |
| Anemia (Hb) | Having fewer red blood cells than normal reducing the amount of oxygen that can be carried in the blood |
| Karnofsky index | A measure of "performance status", or how well patients are able to function - for example, ability to carry on normal activity and self-care, or level of disability |
| ECOG | A measure of "performance status", or how well patients are able to function - ranges from 0 (no symptoms) to 4 (bedbound) for patients that are alive, or 5 for patients that have died. |
| **Risk profile - Disease characteristics** | Cytogenetics | Measurement of how normal or abnormal a patient's chromosomes are - the genetic code of humans is usually packed into 23 pairs of chromosomes, but there may be changes in cancer cells or in the cells of people that are likely to get cancer. |
| Molecular genetics | Analysis of a patient's genes to understand if there are any changes to the genetic code that might make a patient more likely to get a MDS, that might affect how their MDS progresses, or that might help doctors to understand how they will respond to treatment. |
| Tumor activity (LDH) | Lactate dehydrogenase (LDH) is made by normal cells in the body, but the level in the blood is higher in patients with leukemia. Testing LDH levels in the blood can therefore be used to help with the diagnosis of leukemia and to estimate how aggressive it is. |
| **PRO / HR-QoL - general - non-clinical** | Fatigue | Feeling more lethargic and tired than normal / Significant or persistant tiredness that's not proportional to recent activity |
| Sleep changes | Finding it difficult to get to sleep or to stay asleep. |
| Pain | Unpleasant physical sensation, 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 |
| Diarrhea / constipation | Passing looser (sloppier) stools (poo) or passing stools more often than is normal for you / Having difficulty passing stools (poo), which may be small and hard. |
| Nausea | Feeling or being sick, which may lead to impact on intake of food and/or fluids and/or normal activities |
| Anxiety | Feelings of constant worry, or deep concern or uneasy about uncertainties |
| Shortness of breath (Dyspnoea) | Shortness of breath or respiratory problems, which may happen at rest and may limit activities of daily living or self care, and may require treatment |
| Anorexia | Loss of appetite, which may lead to weight loss and malnutrition |
| Cognitive problems | Problems with mental processes of perception, memory, judgment and reasoning |
| Depression | Feelings of severe sadness and unhappiness, often with decreased energy, constant feelings of guilt, doubt or self-blame, worthlessness and hopelessness |
| 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 |
| Infertility | Inability to get pregnant or to produce healthy sperms |
| Hair loss | Alopecia or baldness, loss of hair from part of the head or body |
| Ruptures of capillaries on the legs | due to the lower number of platelets |
| Blood transfusion dependence | transfusion of red blood cells and platelets |
| Stem cells transplantation and GVHD | treatment |
| Increased appreciation of Life | positive change of attitudese towards life in general |
| Good QOL interval (GQI) | Time frame a patient is experiencing good adequate QOL (according to their subjective interpretation using PRO's or answers from QOL tools) |
| Changes in taste and smell | Loss of the senses of smell and taste, including the reduced ability to smell or taste specific substances, for instance, sweet, sour, bitter or salty |
| Sensory neuropathy | Problems involving damage to the peripheral nerves or symptoms of those issues, just like numbness, tingling or burning sensations, increased sensivity to touch, weakness or dysfunction especially of extremities, treatment-associated |
| **PRO / HR-QoL - PRO domains** | 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 |
| Physical function | The effect of MDS or its treatment on day to day physical activities; for example, walking, climbing stairs, driving |
| Social function | The effect of MDS or its treatment on relationships with partner, family and friends including ability to join in with social activities. |
| Role function | The effect of MDS or its treatment on your role; for example, ability to look after children or to work or earn money |
| Financial toxicity | 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 |
| Holidays and travelling | The effect of MDS or its treatment on travelling and active leisure time |
| Eating and drinking | The effect of MDS or its treatment on eating and drinking |
| Work-life / studies | The effect of MDS or its treatment on working or studying |
| Effect on ADL (activities of daily life) | The effect of leukeima or ist treatment on the competence in the daily living, e.g. washing, eating |
| Effect on IADL (instrumental activity of daily life) | The effect of MDS or its treatment on the competence in the instrumental daily living, e.g. shopping, cooking, manage your finances |
| Effect on ADL (activities of daily life) | The effect of leukeima or ist treatment on the competence in the daily living, e.g. washing, eating |
| Effect on IADL (instrumental activity of daily life) | The effect of MDS or its treatment on the competence in the instrumental daily living, e.g. shopping, cooking, manage your finances |
| **Health resource utilization - Resource use** | Hospitalization days | additional days you are in hospital because of MDS or side effects |
| Cost of MDS treatment and care | Money which must be spend on MDS treatment and also additional costs such as taxis or car park costs. |
| Emergency Unit admissions | Frequency that emergency or unplanned hospital treatment is necessary |
| Intensive care admissions | Frequency of requirement for treatment on an intensive care ward due to serious or life threatening disease progression or side-effects |
| Number of outpatient visits | Number of treatment or diagnostic visits in hospital without spending a night there |
| Need of care giver assistance | Requirement for assistance given by caregiver (who could be a family member, friend or a professional care giver) in or outside the hospital |
| Independent living | Ability to live independently, without reliance on carers for daily routine tasks, self-care, trips to hospital or clinical staff house visits |
| Sick leave | Time you cannot work or have active time because of MDS or its treatment |

## ***Framework Evaluation- Outcomes for MM***

|  |  |  |
| --- | --- | --- |
| **DomainName** | **Name** | **HelpText** |
| **Clinical outcome - Time to event** | OS (overall survival) | Length of time that a patient remains alive from either the date of diagnosis or the start of treatment for the myeloma |
| PFS (progression free survival) | Time until someone’s myeloma either gets worse or they die from any cause |
| EFS (event free survival) | Time until someone’s myeloma either gets worse, they die from any cause or they stop their treatment because of side-effects |
| CIR (cumulative incidence of relapse) | Method of calculating the risk of recurring myeloma in a specific time period. |
| DOR (duration of response) | Length of time from responding positively to a treatment to the myeloma starting to recur / to get worse |
| TTP (time to progression) | Time until someone’s myeloma recurs / gets worse (excluding death) |
| TTR (time to response) | Time until first treatment is necessary |
| Treatment free intervall (TFI) | Time from the end of the treatment until the next therapy is needed |
| Time to next treatment TTNT | Time from the end of primary treatment until the institution of the next therapy |
| DSS (disease specific survival) | Time until someone dies from myeloma, but not from other causes. |
| RFS (relapse free survival) | Time from achieving a "complete response", ie a myeloma-free state, to treatment until myeloma recurs. |
| **Clinical outcome - Event type** | Complete Response - CR (complete remission) | Myeloma gets better, resulting in no evidence of plasma cells in tissues or bone marrow and negative immunfixation of serum and urine |
| Partial Response - PR (partial remission) | Myeloma gets better, with a substantial reduction of measuable sites or paraprotein burden compared to levels before treatment, but not enough to qualify as CR |
| Response - Stable disease (SD) | Myeloma stays the same after treatment. The cancer is not getting better or worse |
| Very good partial Response (VGPR) | Good response that fits special criteria. |
| Minimal response (MR) | Treatment was not that effective, but the myeloma showed a response. |
| Clinical relapse | Symptomatic return of myeloma after a patient initially responds well to treatment |
| Biochemical relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a blood test that suggests that myeloma may be recurring |
| Molecular relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a "minimal residual myeloma" test that suggests that myeloma may be recurring |
| Need for chronic therapy | After initial therapy a chronic therapy is needed |
| Cause of death | Death for any reason, whether related to myeloma or not. This records the specific reason for death, not the time until death |
| PD (progressive disease) | Worsening of a patient's myeloma defined by a set of specific criteria |
| **Clinical outcome - Clinical parameter** | 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 |
| Use of Granulocyte colony-stimulating factor (G-CSF) | Treatment given to help a patient to make a certain type of white blood cell called a neutrophil that is sometimes reduced in number because of treatment given or the patient's myeloma |
| Transfusions indepence | Need of red cell or platelet transfusions |
| chronic hemodialysis | Need of chronic hemadialysis |
| Bleeding | Some patients might be more likely to have "bleeding" events such as bruising because of their myeloma or their treatment, which this captures. |
| **Clinical outcome - MRD** | Minimal residual disease (MRD) molecular | The level of myeloma that can be detected as measured by using a DNA sequencing technique |
| Minimal residual disease (MRD) imaging | The level of myeloma that can be detected as measured by using a CT or PET-CT scan |
| Minimal residual disease (MRD) flowcytometric | The level of myeloma that can be detected as measured by using flowcytometry |
| **Safety outcome - AE / Toxicity** | 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 descriptive terminology of adverse events. For each adverse event there is a grading for severity |
| 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 |
| Medication adherence | Patients take their medication as prescribed by the doctor |
| Hematological toxicity | Side-effects that cause changes in the blood or number of blood cells (e.g. anemia, leukopenia, thrombocytopenia, among others) |
| Non-Hematological toxicity | Side-effects that cause changes anywhere other than in the blood, e.g. nausea, neuropathy, mucositis, renal or liver failure, infections |
| SPM (second primary malignancies) | 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 |
| GVHD (graft versus host disease) | Side-effect that can happen after somebody gets a bone marrow or stem cell transplant from somebody else, when the immune cells from the donor attack the body of the person given the transplant. |
| 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 |
| **Risk profile - basic characteristics** | Age | Age is often captured to see if people are more likely to get a myeloma at a certain age, or if people of a certain age do better or worse when treated. |
| Gender | Gender is often captured to see if men or women are more likely to get a myeloma or if their response or survival is different. |
| Renal function | How well the kidneys are working. |
| Anemia (Hb) | Having fewer red blood cells than normal reducing the amount of oxygen that can be carried in the blood |
| Karnofsky index | A measure of "performance status", or how well patients are able to function - for example, ability to carry on normal activity and self-care, or level of disability |
| ECOG | A measure of "performance status", or how well patients are able to function - ranges from 0 (no symptoms) to 4 (bedbound) for patients that are alive, or 5 for patients that have died. |
| **Risk profile - Disease characteristics** | Cytogenetics | Measurement of how normal or abnormal a patient's chromosomes are - the genetic code of humans is usually packed into 23 pairs of chromosomes, but there may be changes in cancer cells or in the cells of people that are likely to get cancer. |
| Molecular genetics | Analysis of a patient's genes to understand if there are any changes to the genetic code that might make a patient more likely to get a myeloma, that might affect how their myeloma progresses, or that might help doctors to understand how they will respond to treatment. |
| **PRO / HR-QoL - general - non-clinical** | Fatigue | Significant or persistant tiredness that's not proportional to recent activity |
| Sleep changes | Finding it difficult to get to sleep or to stay asleep. |
| Pain | Unpleasant physical sensation, 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 |
| Diarrhea | Passing looser stools (poo) or passing stools more often than is normal for you |
| Constipation | Having difficulty passing stools (poo), which may be small and hard |
| Nausea | Feeling or being sick, which may lead to impact on intake of food and/or fluids and/or normal activities |
| Anxiety | Feelings of constant worry, or deep concern or uneasy about uncertainties |
| Shortness of breath (Dyspnoea) | Shortness of breath or respiratory problems, which may happen at rest and may limit activities of daily living or self care, and may require treatment |
| Anorexia | Loss of appetite, which may lead to weight loss and malnutrition |
| Cognitive problems | Problems with mental processes of perception, memory, judgment and reasoning |
| Changes in taste and smell | Loss of the senses of smell and taste, including the reduced ability to smell or taste specific substances, for instance, sweet, sour, bitter or salty |
| Infertility | Inability to get pregnant or to produce healthy sperms |
| Hair loss | Alopecia or baldness, loss of hair from part of the head or body |
| 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 |
| Depression | Feelings of severe sadness and unhappiness, often with decreased energy, constant feelings of guilt, doubt or self-blame, worthlessness and hopelessness |
| Sensory neuropathy | Problems involving damage to the peripheral nerves (those that connect the limbs and organs to the central nervous sysem and control sensation, movement and coordination) or symptoms caused by those issues, including numbness, tingling or burning sensations, increased sensivity to touch, weakness or dysfunction especially of extremities |
| **PRO / HR-QoL - PRO domains** | Role function | The effect of myeloma or its treatment on your role; for example, ability to look after children or to work or earn money |
| Physical function | The effect of myeloma or its treatment on day to day physical activities; for example, walking, climbing stairs, driving |
| 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 |
| Finances | Financial losses because of co-payment for medical treatment and also loss of salary during sick leave, which may include leave taken by a carer |
| Holidays and travelling | The effect of myeloma or its treatment on travelling and active leisure time |
| Eating and drinking | The effect of myeloma or its treatment on eating and drinking |
| Work-life / studies | The effect of myeloma or its treatment on working or studying |
| Effect on ADL (activities of daily life) | The effect of leukeima or ist treatment on the competence in the daily living, e.g. washing, eating |
| Effect on IADL (instrumental activity of daily life) | The effect of myeloma or its treatment on the competence in the instrumental daily living, e.g. shopping, cooking, manage your finances |
| **Health resource utilization - resource use** | Hospitalization days | additional days you are in hospital because of myeloma or side effects |
| Cost of treatment | Money which must be spend on myeloma treatment |
| Emergency Unit admissions | Emergency or unplanned hospital treatment is necessary |
| Intensive care admissions | Requirement for treatment on an intensive care ward due to serious or life threatening disease progression or side-effects |
| Outpatient visits | Treatment or diagnostic visits in hospital without spending a night there |
| Financial toxicity | 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 |
| 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 |
| Sick leave | time you cannot work or have active time because of myeloma or ist treatment |

## ***Framework Evaluation- Outcomes for NHL***

|  |  |  |
| --- | --- | --- |
| **DomainName** | **Name** | **HelpText** |
| **Clinical outcome - Time to event** | OS (overall survival) | Length of time that a patient remains alive from either the date of diagnosis or the start of treatment for the lymphoma |
| PFS (progression free survival) | Time until someone’s lymphoma either gets worse or they die from any cause |
| EFS (event free survival) | Time until someone’s lymphoma either gets worse, they die from any cause or they stop their treatment because of side-effects |
| CIR (cumulative incidence of relapse) | Method of calculating the risk of recurring lymphomain a specific time period. |
| DOR (duration of response) | Length of time from responding positively to a treatment to the lymphoma starting to recur / to get worse |
| TTP (time to progression) | Time until someone’s lymphoma recurs / gets worse (excluding death) |
| TTR (time to response) | Time from starting a treatment until a positive response to treatment is documented |
| TTT (Time to treatment) | Time until first treatment is necessary |
| TFI (Treatment free intervall) | Time from the end of the treatment until the next therapy is needed |
| TTNT (Time to next treatment) | Time from the end of primary treatment until the institution of the next therapy |
| Time to transformation | Time until histologic transformation to an aggressive lymphoma takes place |
| DSS (Disease specific survival) | Time until someone dies from lymphoma, but not from other causes |
| RFS (relapse free survival) | Time from achieving a lymphoma-free state, to treatment until lymphoma recurs |
| **Clinical outcome - Event type** | Complete Response - CR (complete remission) | Lymphoma gets better, resulting in no evidence of abnormally enlarged lymph nodes, spleen or liver. Residual mass is PET-CT negative |
| Partial Response - PR (partial remission) | Lymphoma gets better, with a substantial reduction of measuable sites compared to levels before treatment, but not enough to qualify as CR |
| Response - Stable disease (SD) | Lymphoma stays the same after treatment. The cancer is not getting better or worse |
| Relapse - Clinical relapse | Symptomatic return of lymphoma after a patient initially responds well to treatment |
| Progressive disease (PD) | Worsening of a patient's lymphoma defined by a set of specific criteria |
| Biochemical relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a blood test that suggests that lymphoma may be recurring |
| Molecular relapse | When a patient has had a positive response to treatment, and despite not having any symptoms has a result on a "minimal residual lymphoma" test that suggests that lymphoma may be recurring |
| Need for chronic therapy | After initial therapy a chronic therapy is needed |
| Cause of death | Death for any reason, whether related to lymphoma or not. This records the specific reason for death, not the time until death |
| **Clinical outcome - clinical parameter** | 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 |
| Use of G-CSF | Treatment given to help a patient to make a certain type of white blood cell called a neutrophil that is sometimes reduced in number because of treatment given or the patient's lymphoma |
| Virus reactivation | Reactivation of virus infections, like Herpes simplex (HSV) or some hepatitis viruses (HBV) |
| Response in PET-CT | Response in a specific diagnostic imaging test |
| Bleeding | Some patients might be more likely to have "bleeding" events such as bruising because of their lymphomaor their treatment, which this captures. |
| **Clinical outcome - MRD** | Minimal residual disease (MRD) molecular | The level of lymphoma that can be detected as measured by using a DNA sequencing technique |
| **Safety outcome - AE / Toxicity** | 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 descriptive terminology of adverse events. For each adverse event there is a grading for severity |
| 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 |
| Hematological toxicity | Side-effects that cause changes in the blood or number of blood cells (e.g. anemia, leukopenia, thrombocytopenia, among others) |
| Non-Hematological toxicity | Side-effects that cause changes anywhere other than in the blood, e.g. nausea, neuropathy, mucositis, renal or liver failure, infections |
| SPM (second primary malignancies) | 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 |
| Medication adherence | Patients take their medication as prescribed by the doctor |
| GVHD (graft versus host disease) | Side-effect that can happen after somebody gets a bone marrow or stem cell transplant from somebody else, when the immune cells from the donor attack the body of the person given the transplant. |
| Tumorlysis | Metabolic disorder related to the lymphoma treatment |
| Cardiovascular (heart) toxicity | impaired cardiac or vascular function because of the lymphoma or ist treatment |
| 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 |
| **Risk profile - basic characteristics** | Age | Age is often captured to see if people are more likely to get a lymphoma at a certain age, or if people of a certain age do better or worse when treated. |
| Gender | Gender is often captured to see if men or women are more likely to get a lymphomaor if their response or survival is different. |
| Renal function | How well the kidneys are working. |
| Anemia (Hb) | Having fewer red blood cells than normal reducing the amount of oxygen that can be carried in the blood |
| Karnofsky index | A measure of "performance status", or how well patients are able to function - for example, ability to carry on normal activity and self-care, or level of disability |
| ECOG | A measure of "performance status", or how well patients are able to function - ranges from 0 (no symptoms) to 4 (bedbound) for patients that are alive, or 5 for patients that have died. |
| **Risk profile - disease characteristics** | Cytogenetics | Measurement of how normal or abnormal a patient's chromosomes are - the genetic code of humans is usually packed into 23 pairs of chromosomes, but there may be changes in cancer cells or in the cells of people that are likely to get cancer. |
| Molecular genetics | Analysis of a patient's genes to understand if there are any changes to the genetic code that might make a patient more likely to get a leukemia, that might affect how their lymphoma progresses, or that might help doctors to understand how they will respond to treatment. |
| Tumor activity (LDH) | Lactate dehydrogenase (LDH) is made by normal cells in the body, but the level in the blood is higher in patients with leukemia. Testing LDH levels in the blood can therefore be used to help with the diagnosis of lymphomaand to estimate how aggressive it is. |
| **PRO / HR-QoL - general - non-clinical** | Fatigue | Significant or persistant tiredness that's not proportional to recent activity |
| Sleep changes | Finding it difficult to get to sleep or to stay asleep. |
| Pain | Unpleasant physical sensation, 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 |
| Diarrhea | Passing looser stools (poo) or passing stools more often than is normal for you |
| Constipation | Having difficulty passing stools (poo), which may be small and hard |
| Nausea | Feeling or being sick, which may lead to impact on intake of food and/or fluids and/or normal activities |
| Anxiety | Feelings of constant worry, or deep concern or uneasy about uncertainties |
| Dyspnoea | Shortness of breath, which may happen at rest and may limit activities of daily living or self care, and may require treatment. |
| Anorexia | Loss of appetite, which may lead to weight loss and malnutrition |
| Cognitive problems | Problems with mental processes of perception, memory, judgment and reasoning |
| Depression | Feelings of severe sadness and unhappiness, often with decreased energy, constant feelings of guilt, doubt or self-blame, worthlessness and hopelessness |
| Swelling of arms and legs | Edema in hands, arms, feet, ankles or legs, maybe because of kidney dysfuntion |
| Muscle dysfunction | Lack of muscle strength or e.g. cramps, involuntary contractions or spams that occur in various muscles |
| Changes in taste and smell | Loss of the senses of smell and taste, including the reduced ability to smell or taste specific substances, for instance, sweet, sour, bitter or salty |
| Shortness of breath (Dyspnoea) | Shortness of breath or respiratory problems, which may happen at rest and may limit activities of daily living or self care, and may require treatment |
| Night sweats | Night sweats that make your nightclothes and bed sheets soaking wet, are often described as 'drenching' |
| 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 |
| Infertility | Inability to get pregnant or to produce healthy sperms |
| Hair loss | Alopecia or baldness, loss of hair from part of the head or body |
| Sensory neuropathy | Problems involving damage to the peripheral nerves (those that connect the limbs and organs to the central nervous sysem and control sensation, movement and coordination) or symptoms caused by those issues, including numbness, tingling or burning sensations, increased sensivity to touch, weakness or dysfunction especially of extremities |
| **PRO / HR-QoL - PRO domains** | 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 |
| Physical function | The effect of lymphoma or its treatment on day to day physical activities; for example, walking, climbing stairs, driving |
| Role function | The effect of lymphoma or its treatment on your role; for example, ability to look after children or to work or earn money |
| Financial toxicity | 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 |
| Holidays and travelling | The effect of lymphomaor its treatment on travelling and active leisure time |
| Eating and drinking | The effect of lymphoma or its treatment on eating and drinking |
| Work-life / studies | The effect of lymphomaor its treatment on working or studying |
| Effect on ADL (activities of daily life) | The effect of leukeima or ist treatment on the competence in the daily living, e.g. washing, eating |
| Effect on IADL (instrumental activity of daily life) | The effect of lymphoma or its treatment on the competence in the instrumental daily living, e.g. shopping, cooking, manage your finances |
| **Health resource utilization - resource use** | Hospitalization days | additional days you are in hospital because of lymphomaor side effects |
| Cost of lymphoma treatment | Money which must be spend on lymphoma treatment |
| Emergency Unit admissions | Emergency or unplanned hospital treatment is necessary |
| Intensive care admissions | Requirement for treatment on an intensive care ward due to serious or life threatening disease progression or side-effects |
| 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 |
| Need of care giver assistance | frequency of assistance given by caregiver in or outside the hospital |
| Sick leave | time you cannot work or have active time because of lymphomaor ist treatment |

## ***KOL Preferred Sources of Information***

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| **AML** |
| 1. **Indicate what sources of information should be assessed by a clinical value framework** |
| Randomized clinical trials, real world evidence  Explanation:  For a clinical value framework it will be very important to collect real world evidence, i.e. how drugs behave in routine clinical setting in a patient cohort that has not been selected/biased based on very good performance status etc.  Real world data should be collected from registries/registry studies, or from large clinical centers treating respective patient cohorts (large single center experience data).  However, the respective data should be compared to data collected within randomized clinical trials, which usually form the basis for the approval of drugs; to determine the real clinical value of novel drugs / drug combinations, improved outcome should be also seen in a real world setting.  Data from randomized trials is needed in order to define the maximum benefit one can expect from a respective drug / drug combination in an ideal setting, i.e. a relatively uniform, well-defined patient cohort; similar starting points for patients who are all in “good shape”, e.g. good ECOG, no significant concomitant disease, etc.  Registry / large single center data are needed to better capture clinical value in a real world setting, i.e. benefit in older patients with more comorbidities, use in patients with more “leukemia-associated” symptoms (e.g. patients with active infections). " |
| 1. **Would you consider different sources for specific AML patient populations?** |
| No  Explanation:  For all indications, data from clinical trials should be compared to respective real-world data sets, in order to be able to determine the impact of respective studies in a routine clinical setting with an unbiased cohort of patients. Respective analyses will also allow to determine better for which patient population respective therapies are relevant / feasible. In case, a new drug has performed well within a clinical trial but is never really used in a routine clinical setting, as e.g. patients do not qualify for the respective treatment as the target population is usually in a very poor condition, this information could be used to rethink the indication of a respective treatment protocol.  In order to assess drug safety, in my opinion we do also need both clinical trial and real world data, that will allow to get a better understanding of how well a novel treatment is tolerated, accepted with regard to compliance, and causing side effects. Real world / registry data will be more accurate with regard to daily clinical routine, but can then of course also show the power / impact of controlled settings that can be very beneficial for patients." |
| **3) Indicate which standard measurement criteria/instruments for quality of life you consider appropriate for AML patients**  -> A clinical value framework should definitely include studies with availability of QoL data. Especially in older AML patient populations outcome with regard to leukemia-free survival should be focused on an outcome with good QoL rather than only a very long leukemia-free survival, which is often only achieved on the basis of a very strenuous aggressive therapy strategy that might not pay off in net weighing the loss of QoL during therapy with lifetime gained by the respective treatment strategy.  -> Ideally, respective studies would have data available from PROMs, but determination through standard QoL assessments (see below).  LIST OF INSTRUMENTS  -> QoL  EORTC-QLQ-C30[[1]](#footnote-1)  EORTC-QLQ-BR23[[2]](#footnote-2)  -> Psycho-oncology  EORTC-QLQ-FA12[[3]](#footnote-3)  -> Fear of progression  PA-F[[4]](#footnote-4)  -> Anxiety/Depression  HADS[[5]](#footnote-5) |
| **CLL** |
| **1) Indicate what sources of information should be assessed by a clinical value framework** |
| Randomized clinical trials, Registries, Electronic medical records, Collaborative projects (including databases collecting information used in ERIC projects), QoL questionnaires, Observational/Phase IV studies  Explanation:  Randomized clinical trials: collecting information on efficacy of standard and experimental treatments, safety profile, quality of life;  Registries: collecting information on patient characteristics at diagnosis and/or at different stages of disease;  Electronic medical records: collecting information on laboratory tests, treatments administered, medical resources use;  Collaborative projects (including databases collecting information used in ERIC projects): collecting information on different treatments in terms of safety profile and efficacy in clinical practice;  Quality of life questionnaires: collecting information on quality of life;  Observational/ Phase IV studies: collecting information on efficacy and safety of different treatments in clinical practice |
| 1. **Would you consider different sources for specific CLL patient populations?** |
| NO |
| **3) Indicate which standard measurement criteria/instruments for quality of life you consider appropriate for CLL patients**  Validated quality of life questionnaires: EORTC-QLQ-C30; EORTC QLQ-CLL17, EuroQol EQ5D  Use of medical resources (hospital visits, doctor visits, hospitalization, treatments, investigations) |
| **4) Indicate additional Real World information/ data that you would consider useful and to be added** |
| In addition to data from randomized clinical trials, real world information/data that would provide relevant insights includes: Safety profile (including AEs, treatment interruption and discontinuation, dose reduction) in clinical practice (usually involving patients with more severe comorbidities compared to those enrolled in randomized clinical trials) Use of medical resources (including hospital and doctor visits, need for transfusion support, investigations performed, supportive care, treatment administered) Efficacy (also in this regard it should be taken into consideration that patients treated in clinical practice carry more severe comorbidities compared to those enrolled in randomized clinical trials) Patient preferences and quality of life (this information can be collected in observational studies using different methodologies, including quality of life questionnaires, discrete choice experiment -DCE- approach) Larger cohorts of patients treated in clinical practice in well-annotated database allow more robust multivariate analysis taking into account several disease-, patient- and treatment-related factors. |
| **MDS** |
| **1) Indicate what sources of information should be assessed by a clinical value framework** |
| Randomized clinical trials, then health authority registries and real world data from studies with relevant number of cases or national registries of MDS  Explanation:  Randomized studies are controlled studies providing objective data  Health authority registries ( like AIFA) can give information on specific drugs  MDS Registry give information on epidemiology and demographic and clinical characteristics of patients |
| 1. **Would you consider different sources for specific MDS patient populations?** |
| Yes |
| 1. **Indicate each patient population profile and the respective sources** |
| MDS patients with age < 50 years, ( genetists, pediatric registries)  Dysplastic CMML ( MDS/MPN registry and randomized studies) |
| **4) Indicate which standard measurement criteria/instruments for quality of life you consider appropriate for MDS patients** |
| QOL-E ( specific for MDS) pub Oliva et al 2002  EQ-5D is another standardized instrument  Molecular studies for the young MDS category |
| **5) Indicate additional Real World information/ data that you would consider useful and to be added** |
| epidemiologic data of registries to educate the patients on their diseases |
| **MM** |
| **1) Indicate what sources of information should be assessed by a clinical value framework** |
| Randomized clinical trials data, non-interventional real world studies (registries and observational studies)  Explanation:  Randomized clinical trials data are key in order to approve a new drug/combination and to obtain a demonstration of efficacy and safety in a pre-defined patient population. Post-approval, non-interventional studies are important for ongoing value demonstration, evaluations of comparative cost/effectiveness and the vigilant monitoring of drug safety. This can be obtained by registries or observational studies using real world data (a good monitoring plan of obtained data is mandatory).  Moreover, the inclusion in these studies of patients usually excluded from clinical trials is another reason to underline the need of real-world data. Registries and non-interventional studies are also very useful in order to analyze the current practice each country (this can be very heterogeneous) and to analyze the current sequencing therapies. |
| 1. **Would you consider different sources for specific MM patient populations?** |
| No |
| 1. **Indicate each patient population profile and the respective sources** |
| There is no enough evidence in order to justify a different clinical value framework evaluation between different MM patient populations |
| **4) Indicate which standard measurement criteria/instruments for quality of life you consider appropriate for MM patients** |
| EORTC QLQ-C30, QLQ-MY20, EQ5D, FACT MM, QLQ-CIPN20, FACIT-Fatigue, FACT-NTx (as defined in Sonneveld Leukemia (2013) 1959 – 1969) |
| **5) Indicate additional Real World information/ data that you would consider useful and to be added** |
| From a patients’ perspective, non-interventional real world studies should consider the time spent in the hospital by the patient (how many days/month? How many hours?), the interference of the therapy with patients’ life (e.g. young patient that still go to work), the impact of long-lasting side effects (e.g. neuropathy). Moreover, since MM therapies are long-lasting, more data on the cost of drugs and hospital resources utilization is needed in MM |
| **NHL** |
| **1) Indicate what sources of information should be assessed by a clinical value framework** |
| Prospective clinical trials, retrospective trials/registry data  Explanation:  RCT = limited bias  retrospective trials/ registry data = more representative of general patient population |
| 1. **Would you consider different sources for specific NHL patient populations?** |
| For RCT, preferred in general. Retrospective trial and registry data are preferred in patients excluded from studies (medical non-fit, HIV+), or with rare disease/comorbidities |
| **3) Indicate which standard measurement criteria/instruments for quality of life you consider appropriate for MM patients** |
| EORTCQLQ30 or lymphoma specific questionnaires. However, the exact impact of metric changes is not yet very clear |
| **4) Indicate additional Real World information/ data that you would consider useful and to be added** |
| Based on registries: medically un-fit patient, impact of comorbidities, sequence of treatment |

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