Treatment-Related Mortality Designation System

Training Manual

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1.0 Introduction

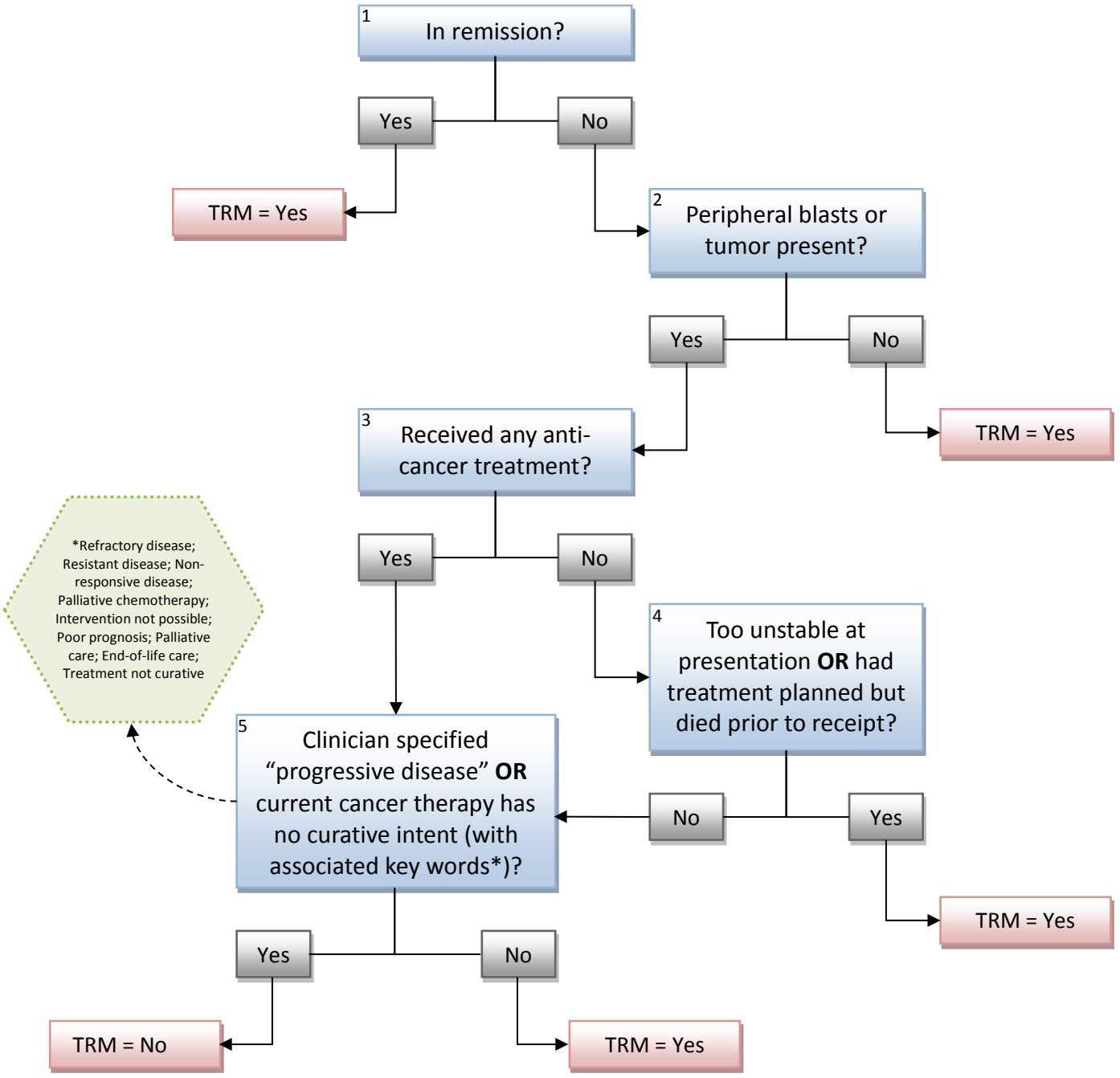
Treatment-related mortality (TRM) is an important endpoint in pediatric cancer and hematopoietic stem cell transplantation (HSCT) clinical trials. However, TRM has been inconsistently defined in the literature. This manual describes how to apply a TRM definition and cause-of-death attribution system that was developed and validated for this population by an international group of supportive care experts.[1] With this system, TRM is defined by death occurring in the absence of progressive cancer. This approach is important as many children with refractory disease will die from toxicities of therapy.

1. Alexander S, Pole JD, Gibson P, et al. Classification of treatment-related mortality in children with cancer: a systematic assessment. Lancet Oncol. 2015;16: e604-610.

2.0 TRM Designation System

A TRM designation system flow chart facilitates determining a patient's TRM designation status. The flow chart is guided by 5 key binary questions which are described in greater detail below. Each of the 5 questions should evaluate status at the time of the patient's death. However, there is no time restriction on how far back data abstractors can go in the patient's treatment history in order to obtain the necessary information.

Figure 1: TRM Designation System Flow Chart



1) In Remission?

- Determine whether the patient is in remission at the time of death
- If the patient is known to be in remission at the time of death, then select 'Yes' and TRM designation = Yes
  - Documentation specifically describing "remission" or confirmation on pathology can be used to determine remission status
- Some patients with leukemia may die during induction before a bone marrow aspiration to assess treatment response is performed. Similarly, solid tumor patients may undergo a resection and die early in therapy before re-staging can occur. In these cases, remission status cannot be definitely assessed. If this is the case, move to question 2

2) Peripheral Blasts or Tumor Present?

- Determine whether there is presence of peripheral blasts or tumor present at the time of death
- When remission status cannot be definitely assessed (as described above), the flow chart asks whether disease is grossly present, either on imaging for solid or brain tumors, or by peripheral complete blood count (CBC) for leukemia patients. If no tumor is grossly present (for example, completely resected) or peripheral blasts have disappeared, select 'No' and TRM designation = Yes
  - If there are too few white blood cells on the CBC to perform a differential count, then assume there are no peripheral blasts present, select 'No' and TRM designation = Yes
  - While there is no time relative to death requirement for question 2, it is anticipated that the absence of grossly present tumor or peripheral blasts will be relatively close to death
- If tumor or peripheral blasts is present, select 'Yes' and move to question 3

3) Received Any Anti-Cancer Treatment?

- Determine whether the patient has ever received any anti-cancer treatment
- Anti-cancer treatment may be chemotherapy, surgery to remove cancer or radiotherapy
- If the patient has never received any anti-cancer treatment, select 'No' and move to question 4
- If the patient has received anti-cancer treatment at any point, select 'Yes' and move to question 5

4) Too Unstable at Presentation OR had Treatment Planned but Died Prior to Receipt?

- Some patients die before cancer treatment can be provided
- If the medical record indicates that the reason the patient did not receive cancer treatment was because either: (1) the patient was too unstable to tolerate treatment OR (2) a treatment plan was described but the patient died before it could be administered, select 'Yes' and TRM designation = Yes
- If neither of the above two conditions are met, select 'No' and move to question 5

5) Clinician Specified "Progressive Disease" OR Current Cancer Therapy has no Curative Intent (with Associated Key Words*)?

- This category is usually the most difficult to determine
- When clinical curative treatment is withdrawn due to poor prognosis, associated key words must refer to cancer specifically rather than poor prognosis due to progressive infection or poor organ function, as examples

- **Key Words that Indicate Progressive Cancer***: Refractory disease; Resistant disease; Non-responsive disease; Palliative chemotherapy; Intervention not possible; Poor prognosis; Palliative care; End-of-life care; Treatment not curative
- For most patients who die during profound chemotherapy-associated myelosuppression (for example, absolute neutrophil count < 100 /uL) select 'No' and TRM designation = Yes, unless the medical record states the patient has progressive cancer*. Similarly, for most patients who die during the transplant procedure (before engraftment or shortly after engraftment), select 'No' and TRM designation = Yes unless the medical record states the patient has progressive cancer*

- If a patient receives aggressive chemotherapy, is myelosuppressed AND has documentation in the medical record of progressive cancer* or terminology of palliative chemotherapy, consider the patient to have progressive cancer, select 'Yes' and TRM designation = No

3.0 Cause-of-Death Attributions

- **Figure 2** describes the TRM cause-of-death attributions
- The cause-of-death attribution system is intended for use in TRM cases only
- For each cause-of-death attribution, check off one of the response categories - probable, possible or not present
- Patients may meet multiple criteria within each cause-of-death attribution category and all criteria that apply should be recorded
- Patients may have a probable and possible designation for the same cause-of-death attribution category (for example hemorrhage) but not the same specific event. For example, a patient may have a probable for intracranial hemorrhage and possible for pulmonary hemorrhage but should not have both probable and possible for pulmonary hemorrhage
- In order to determine whether events are present which meet criteria for a probable or possible cause-of-death attribution, evaluate medical records for 14 days prior to death. If the medical records 14 days prior to death indicate a relevant event occurring more distal to death, such as invasive fungal infection, review the medical records preceding the 14 day window to identify enough information about that event so that it may be adequately coded
- Abstractors should be cautious that laboratory “normal” values may differ by age, gender and institutions and therefore “Upper limits of normal” should be noted for each patient

Figure 2: TRM cause-of-death attributions

Cause-of-death Attribution *14 days prior to death			
	Probable	Possible	Not Present
Infections	□ Clinically or radiographically documented infection with associated microbiologically documented organism	□ Clinically or radiographically documented infection without associated microbiologically documented organism	❑
Hemorrhage	□ Acute symptomatic intracranial hemorrhage demonstrated by imaging or pathology □ Acute symptomatic pulmonary hemorrhage demonstrated by imaging or pathology □ Acute symptomatic bleeding resulting in hypotension or urgent transfusion or fluid bolus	□ Acute symptomatic pulmonary hemorrhage without demonstration by imaging or pathology	❑
Thrombosis	□ Acute symptomatic intracranial thrombosis or embolism demonstrated by imaging or pathology □ Acute symptomatic pulmonary thrombosis or embolism demonstrated by imaging or pathology □ Acute symptomatic hepatic thrombosis or embolism demonstrated by imaging or pathology	□ Acute symptomatic pulmonary thrombosis or embolism without demonstration by imaging or pathology	❑
Cardiac System **exclude terminal event*	□ Acute symptomatic arrhythmia excluding sinus tachycardia/bradycardia demonstrated by electrocardiogram □ Acute symptomatic cardiac dysfunction defined by echocardiogram or cardiac imaging or pathology	□ Acute symptomatic arrhythmia excluding sinus tachycardia/bradycardia without demonstration by electrocardiogram	❑
Immune Mediated	□ Acute, allergic reaction or anaphylaxis with symptomatic bronchospasm or edema/angioedema or hypotension □ Worsening symptomatic graft versus host disease □ Acute symptomatic hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome or cytokine-release syndrome	□ Stable graft versus host disease	❑
Metabolic	□ Clinically diagnosed tumor lysis syndrome with cardiac arrhythmia or seizure or creatinine > 3x ULN		❑
Nervous System	□ Acute symptomatic central nervous system necrosis demonstrated by imaging or pathology □ Acute symptomatic encephalopathy demonstrated by imaging or electroencephalography □ Acute symptomatic hemorrhage or stroke demonstrated by imaging or pathology □ Acute symptomatic hydrocephalus or raised intracranial pressure demonstrated by imaging or pathology or measurement of intracranial pressure □ Seizure lasting at least 30 minutes within 48 hours of death	□ Acute symptomatic central nervous system necrosis without demonstration by imaging or pathology □ Acute symptomatic encephalopathy without demonstration by imaging or electroencephalography □ Acute symptomatic hemorrhage or stroke without demonstration by imaging or pathology □ Acute symptomatic raised intracranial pressure without demonstration by imaging or pathology or measurement of intracranial pressure □ Seizure lasting 5 - <30 minutes within 48 hours of death	❑
Respiratory System	□ Acute symptomatic respiratory distress leading to ventilator support such as intubation, or other mechanisms of pressure support including BIPAP and CPAP	□ Acute symptomatic respiratory distress without ventilator support **Note: Exclude terminal event*	❑
GI System	□ Acute symptomatic bowel pathology resulting in necrosis or obstruction or perforation demonstrated by imaging or pathology □ Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin > 10x ULN or high ammonium > 2.5x ULN or INR > 2.5x ULN □ Acute clinically diagnosed pancreatitis with hemorrhage or peritonitis or necrosis or hemodynamic instability (evidenced by hypotension or urgent transfusion or fluid bolus or vasopressors)	□ Acute symptomatic bowel pathology resulting in necrosis or obstruction or perforation without demonstration by imaging or pathology □ Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin >1.5 to ≤10x ULN or INR >1.5 to ≤2.5x ULN or ammonium >1.5 to ≤2.5x ULN	❑
Renal System	□ Acute kidney injury with dialysis/renal replacement therapy planned or received		❑
External Causes	□ Unintentional injury (e.g. accident) □ Suicide □ Homicide		❑

Definitions: Acute – must have occurred within 14 days prior to death; GI – gastrointestinal; Symptomatic – showing symptoms (for example, for GI could be pain, abdominal distention or bloody stool)

3.1 Infections

- In order to code an infection, signs or symptoms must be present. For example, a positive skin swab should not be coded if there are no associated symptoms
- Do not record the following:
    - Bacteria (other than *Shigella*, *Salmonella, Campylobacter* or *Clostridium difficile* toxin) or fungi from stool
    - Bacteria or yeasts from broncho-alveolar lavage, endo-tracheal tube (ETT) or mouth swabs
    - Bacteria or yeasts obtained post-mortem

3.2 Hemorrhage

- To determine if Probable Pulmonary Hemorrhage cause-of-death attribution criteria are met, look to see if a chest radiology report includes the possibility of hemorrhage in the differential diagnosis
- If the patient has a symptomatic intracranial hemorrhage, also indicate a Probable Nervous System cause-of-death attribution (*acute symptomatic hemorrhage or stroke)*. This is the only instance in which the same event is coded in two places in the cause-of-death attribution system
- In order for acute symptomatic bleeding to result in hypotension, the volume of blood must be very large. Thus, bleeding of this magnitude will usually be GI bleeding. Bleeding from nose (epistaxis), mouth (mucositis) and presence of blood in urine will rarely result in sufficient blood loss to cause hypotension
- "Urgent transfusion" is defined as the transfusion of packed red blood cells only, and not urgent transfusion of platelets or other blood products, even though they might be administered to treat hemorrhage. Packed red blood cells are often given routinely when hemoglobin drops below 70 g/L and these instances should not be considered urgent transfusions for hemorrhage unless the medical record clearly states otherwise

3.3 Thrombosis

- Symptoms of hepatic thrombosis or embolism include pain, jaundice and ascites

3.4 Cardiac System

- Symptoms of acute symptomatic cardiac dysfunction include fatigue, shortness of breath, exercise intolerance, tachycardia (fast heart beat), hypotension (low blood pressure) and poor perfusion
- Ejection fraction < 50% may signify systolic dysfunction
- Do not consider diastolic dysfunction when coding a Cardiac System cause-of-death attribution
- Exclude terminal event when coding a Cardiac System cause-of-death attribution
    - For example, if a patient dies of sepsis and the last event prior to death is cardiac arrest, this should not be coded as a Cardiac System cause-of-death attribution as it would be considered a terminal event

3.5 Immune Mediated

- Documentation of worsening graft versus host disease (GVHD) includes a description of uncontrolled GVHD, escalated interventions for GVHD (such as steroids and immunosuppressive medications) and increasing GVHD

- A diagnosis of hemophagocytic lymphohistiocytosis (HLH) or macrophage activation system must be stated in the medical record. Hemophagocytosis may be seen in a bone marrow aspiration in the absence of an HLH diagnosis

3.6 Metabolic

- In order to code tumor lysis syndrome, the exact wording (or "TLS") must be present in the medical record; an increase in creatinine alone is not sufficient

3.7 Nervous System

- Necrosis is not synonymous with atrophy or infarct
- Encephalopathy must be explicitly stated in the medical record
- If the patient has an acute symptomatic hemorrhage or stroke, also indicate a Probable Hemorrhage cause-of-death attribution (*acute symptomatic intracranial hemorrhage*). This is the only instance in which the same event is coded in two places in the cause-of-death attribution system
- Seizure lasting at least 30 minutes within 48 hours of death can include multiple seizures when added together, and would fulfill the criteria for a Probable Nervous System cause-of-death attribution

3.8 Respiratory System

- There must be presence of symptoms of respiratory distress, such as increased oxygen requirement, fast breathing (tachypnea), or difficulty with breathing (dyspnea), in addition to ventilation support. Intubation alone is not sufficient. For example, a patient who is intubated for seizures without any respiratory distress does not meet criteria for a Respiratory System cause-of-death attribution
- Examples of ventilator support include BIPAP (bilevel positive airway pressure), CPAP (continuous positive airway pressure) and HFOV (high frequency oscillatory ventilation)
- Oxygen by nasal prongs or face mask are not considered ventilator support
- Exclude terminal events when coding a Respiratory System cause-of-death attribution

3.9 GI System

- Examples of bowel pathology include colitis, entercolitis, typhlitis and pneumatosis intestinalis
- Symptoms to consider for "symptomatic bowel pathology" include pain, abdominal distention or bloody stool
- Bowel pathology resulting in bowel resection or creation of an ostomy is sufficient to code a Probable GI System cause-of-death attribution. In this instance, presence of necrosis, obstruction or perforation is not required
- Hepatic dysfunction is synonymous with hepatic impairment

3.10 Renal System

- If the patient has acute kidney injury and dialysis was either planned or considered necessary but not performed for any reason, this documentation in the medical record is sufficient to meet criteria for a Probable Renal System cause-of-death attribution

3.11 External Causes

- Surgical complications should not be reported as accidents
- Examples of External Causes attributions include car accidents or other unintentional injuries, suicide or homicide

4.0 Training Case 1

CASE SUMMARY	
Age at initial diagnosis:	5 years
Time from initial diagnosis to death:	3.5 years
Diagnosis:	Acute lymphoblastic leukemia
Last treatment protocol:	FLAG
Time between last treatment and death	3 months
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

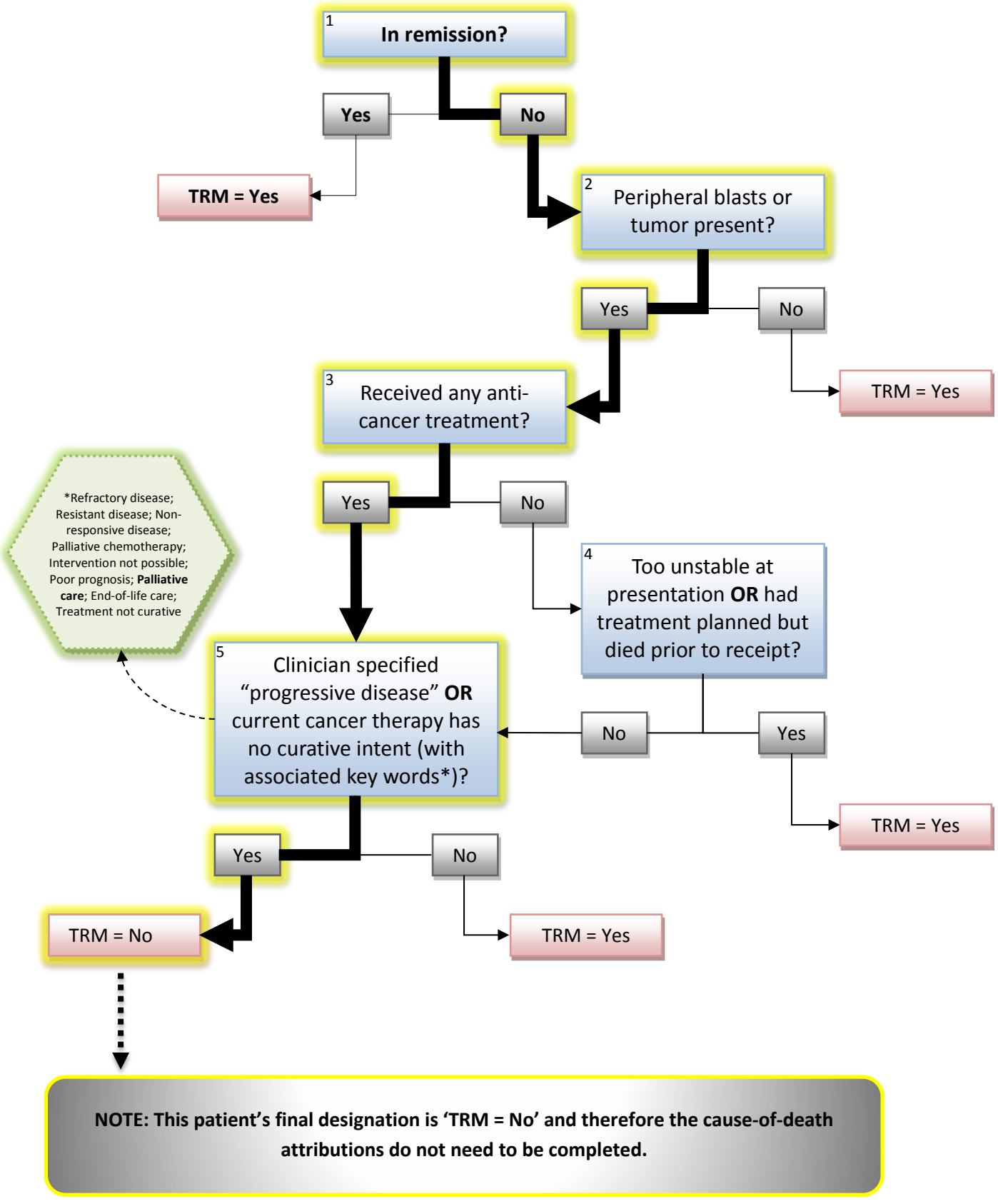
This patient was diagnosed with acute lymphoblastic leukemia at 5 years of age and was treated according to POG 9605. The patient completed induction chemotherapy and achieved morphological remission. The patient completed treatment as per protocol. However at routine check-up shortly after completion of therapy, peripheral blasts were noted and a bone marrow aspirate confirmed relapse. Despite subsequent treatment with salvage chemotherapy, the patient's disease continued to progress and palliative care was initiated.

Treatment Summary 14 days Prior to Death:

The patient was admitted to hospital 10 days prior to death for pain management. Morphine infusion was administered. The patient died peacefully in hospital with family present.

Labs:

	14 Days Prior to Death
WBC	Below lower limit of normal, peripheral blasts present
Absolute Neutrophil Count	750 /uL
Conjugated bilirubin	Normal
Ammonium	Normal
INR	Normal
Creatinine	Normal


1
In remission?
Yes
No
TRM = Yes
2
Peripheral blasts or tumor present?
Yes
No
TRM = Yes
3
Received any anti-cancer treatment?
Yes
No
*Refractory disease; Resistant disease; Non-responsive disease; Palliative chemotherapy; Intervention not possible; Poor prognosis; **Palliative care**; End-of-life care; Treatment not curative
4
Too unstable at presentation **OR** had treatment planned but died prior to receipt?
No
Yes
TRM = Yes
5
Clinician specified "progressive disease" **OR** current cancer therapy has no curative intent (with associated key words*)?
Yes
No
TRM = No
TRM = Yes
NOTE: This patient's final designation is 'TRM = No' and therefore the cause-of-death attributions do not need to be completed.

5.0 Training Case 2

CASE SUMMARY	
Age at initial diagnosis:	15 years
Time from initial diagnosis to death:	3 months
Diagnosis:	Acute myeloid leukemia
Last treatment protocol:	AAML03P1
Time between last treatment and death	10 days
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

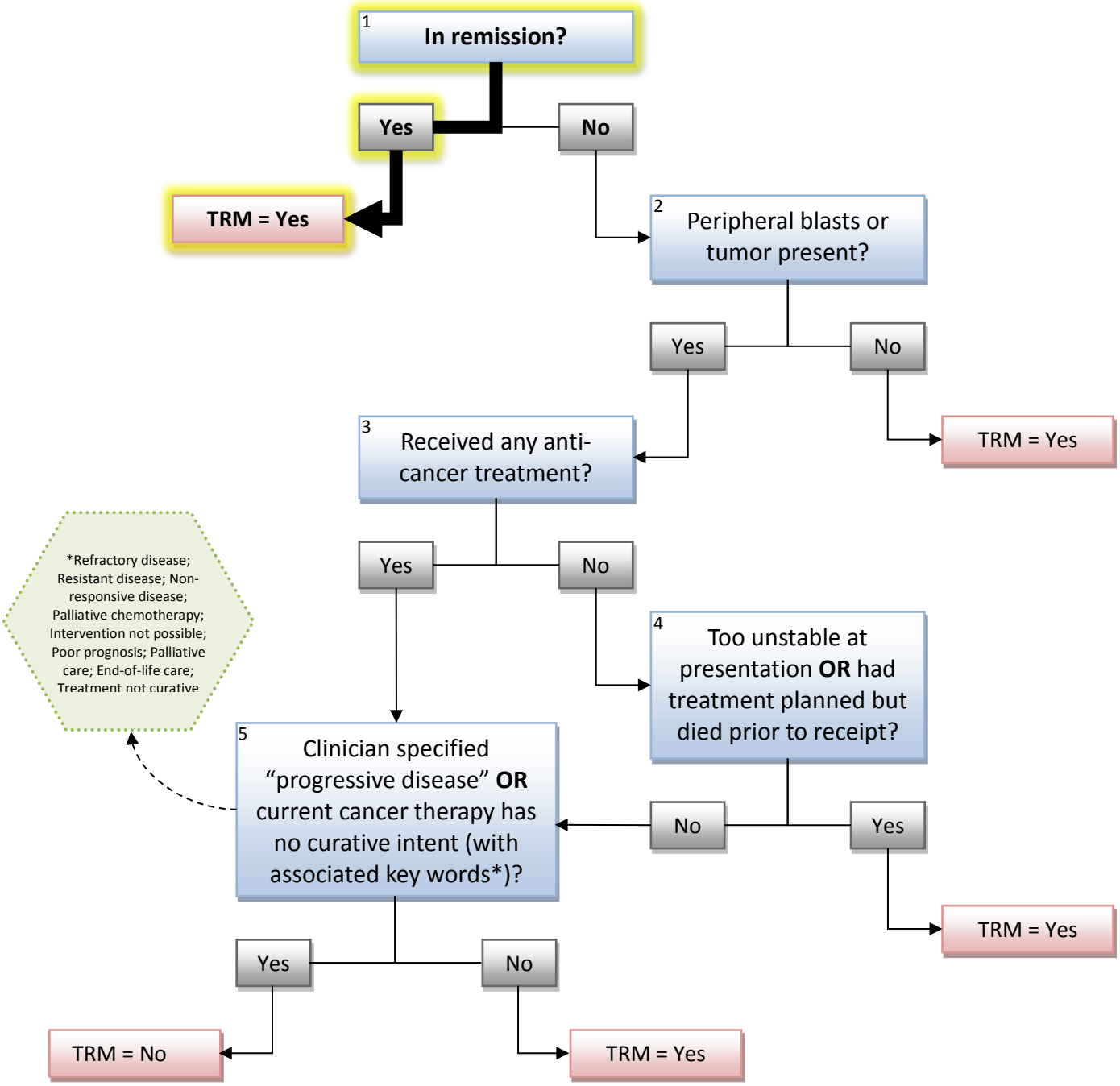
This patient was diagnosed with acute myeloid leukemia at 15 years of age and was treated according to AAML03P1. The patient received two cycles of induction chemotherapy and was in complete morphological remission at the end of Induction 1 and Induction 2. The patient received Intensification 1 uneventfully and was discharged home. Five days later, the patient presented to the emergency department with cough and fever. The patient was admitted and started on broad spectrum antibiotics.

Treatment Summary 14 days Prior to Death:

Fever and cough worsened despite broad spectrum antibiotic therapy. Chest x-ray and CT demonstrated pneumonia and a broncho-alveolar lavage grew *Aspergillus* species. The infection rapidly progressed in spite of three antifungal medications with the patient requiring intubation and high frequency oscillation due to respiratory distress. A family meeting was held and it was decided to not escalate care and to not perform chest compressions if the patient experienced a cardiac arrest. While on the oscillator, the patient's oxygen began to drop and asystole occurred. No resuscitation efforts were made and the patient died shortly thereafter.

Labs:

	14 Days Prior to Death
WBC	Normal, no peripheral blasts present
Absolute Neutrophil Count	Normal
Conjugated bilirubin	Normal
Ammonium	Normal
INR	1.5 times above upper limit of normal
Creatinine	Normal



NOTE: This patient's final designation is 'TRM = Yes' and therefore the cause-of-death attributions must be completed.

Cause-of-Death Attribution *14 days prior to death			
	Probable	**Possible**	**Not Present**
Infections	☑ Clinically or radiographically documented infection with associated microbiologically documented organism	□ Clinically or radiographically documented infection without associated microbiologically documented organism	❑
Hemorrhage	□ Acute symptomatic intracranial hemorrhage demonstrated by imaging or pathology □ Acute symptomatic pulmonary hemorrhage demonstrated by imaging or pathology □ Acute symptomatic bleeding resulting in hypotension or urgent transfusion or fluid bolus	□ Acute symptomatic pulmonary hemorrhage without demonstration by imaging or pathology	☑
Thrombosis	□ Acute symptomatic intracranial thrombosis or embolism demonstrated by imaging or pathology □ Acute symptomatic pulmonary thrombosis or embolism demonstrated by imaging or pathology □ Acute symptomatic hepatic thrombosis or embolism demonstrated by imaging or pathology	□ Acute symptomatic pulmonary thrombosis or embolism without demonstration by imaging or pathology	☑
Cardiac System ***exclude terminal event***	□ Acute symptomatic arrhythmia excluding sinus tachycardia/bradycardia demonstrated by electrocardiogram □ Acute symptomatic cardiac dysfunction defined by echocardiogram or cardiac imaging or pathology	□ Acute symptomatic arrhythmia excluding sinus tachycardia/bradycardia without demonstration by electrocardiogram	☑
Immune Mediated	□ Acute, allergic reaction or anaphylaxis with symptomatic bronchospasm or edema/angioedema or hypotension □ Worsening symptomatic graft versus host disease □ Acute symptomatic hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome or cytokine-release syndrome	□ Stable graft versus host disease	☑
Metabolic	□ Clinically diagnosed tumor lysis syndrome with cardiac arrhythmia or seizure or creatinine > 3x ULN		☑
Nervous System	□ Acute symptomatic central nervous system necrosis demonstrated by imaging or pathology □ Acute symptomatic encephalopathy demonstrated by imaging or electroencephalography □ Acute symptomatic hemorrhage or stroke demonstrated by imaging or pathology □ Acute symptomatic hydrocephalus or raised intracranial pressure demonstrated by imaging or pathology or measurement of intracranial pressure □ Seizure lasting at least 30 minutes within 48 hours of death	□ Acute symptomatic central nervous system necrosis without demonstration by imaging or pathology □ Acute symptomatic encephalopathy without demonstration by imaging or electroencephalography □ Acute symptomatic hemorrhage or stroke without demonstration by imaging or pathology □ Acute symptomatic raised intracranial pressure without demonstration by imaging or pathology or measurement of intracranial pressure □ Seizure lasting 5 - <30 minutes within 48 hours of death	☑
Respiratory System	☑ Acute symptomatic respiratory distress leading to ventilator support such as intubation, or other mechanisms of pressure support including BIPAP and CPAP	□ Acute symptomatic respiratory distress without ventilator support **Note: Exclude terminal event*	❑
GI System	□ Acute symptomatic bowel pathology resulting in necrosis or obstruction or perforation demonstrated by imaging or pathology □ Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin > 10x ULN or high ammonium > 2.5x ULN or INR > 2.5x ULN □ Acute clinically diagnosed pancreatitis with hemorrhage or peritonitis or necrosis or hemodynamic instability (evidenced by hypotension or urgent transfusion or fluid bolus or vasopressors)	□ Acute symptomatic bowel pathology resulting in necrosis or obstruction or perforation without demonstration by imaging or pathology □ Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin >1.5 to ≤10x ULN or INR >1.5 to ≤2.5x ULN or ammonium >1.5 to ≤2.5x ULN	☑
Renal System	□ Acute kidney injury with dialysis/renal replacement therapy planned or received		☑
External Causes	□ Unintentional injury (e.g. accident) □ Suicide □ Homicide		☑

Appendix 1. Frequently Asked Questions

1. ***How can a patient who dies prior to receiving any cancer treatment be designated as having <u>treatment</u> related mortality (TRM = Yes), if they have in fact never received any treatment?***

   TRM is defined as "death occurring in the absence of progressive cancer." In this system, treatment is defined more broadly as any care provided for the patient.

2. ***What if a patient dies very soon after their initial presentation?***

   For patients who die soon after initial presentation, it is most important to identify whether progressive cancer is present at death rather than whether cancer is present at death. For example, some patients with leukemia may have very high white blood cell counts at presentation. If chemotherapy is started and their white blood cell count is falling, then they do not have progressive cancer even if leukostasis is the cause of death and therefore TRM designation = Yes. Similarly, in patients who die of bleeding without evidence of progressive cancer prior to starting treatment, TRM designation = Yes. It is important to assume a patient has died of progressive cancer *<u>only if this specific notation is mentioned</u>*.

3. ***How do I know if the current cancer treatment has no curative intent?***

   In order to assume the current cancer treatment has no curative intent, there must be documented presence of cancer along with a decision to stop cancer treatment that was being given with curative intent. Documentation that states that cancer-directed treatment is not curative is also evidence to support this assumption. Cancer treatments that are referred to as "palliative chemotherapy" typically do not have curative intent.

4. ***It is difficult to tell whether or not the patient died of progressive disease – what do I do?***

   If the clinical findings surrounding cause of death could be either progressive cancer or non-disease-related death, indicate what the medical record favors. If the documentation in the medical record does not clearly favor one or the other, choose TRM designation = Yes.

5. ***How can I tell when bleeding is severe enough to warrant coding the Hemorrhage cause-of-death attribution?***

   Microscopic bleeding (for example, in urine sample or stool specimen) is not enough to cause severe hemorrhage and there must be blood visible clinically. For pulmonary hemorrhage, visualization on broncho-alveolar lavage is not enough to code a Pulmonary Hemorrhage cause-of-death attribution and gross bleeding must be documented in the medical record.

6. ***Is there a place to document if a patient has HLH?***

   Yes, if a patient has a confirmed diagnosis of HLH this should be coded as a Probable Immune Mediated cause-of-death attribution.

7. ***Don't all patients who die have cardiac and respiratory dysfunction just prior to death?***

   Cause-of-death attributions should not capture terminal events. Terminal events are events that occur just before death.

Appendix 2. Practice Cases

PRACTICE CASE #1

CASE SUMMARY	
Age at initial diagnosis:	9 years
Time from initial diagnosis to death:	6 years
Diagnosis:	Precursor B-cell acute lymphoblastic leukemia
Last treatment protocol:	Etoposide
Duration of last treatment:	3 months
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

This patient was diagnosed with standard risk precursor B-cell acute lymphoblastic leukemia and was treated according to POG 9605. The patient completed treatment uneventfully and continued to demonstrate no evidence of disease until 3 years following completion of therapy when routine bloodwork revealed peripheral blasts. Relapse was confirmed by bone marrow aspiration.

Following relapse, the patient was treated with multiple relapse regimens. However, the patient's disease was refractory to all treatment and the patient and family emphasized a desire for symptom management and maximization of quality of life. Following this decision, the patient was placed on oral etoposide and discharged home.

Treatment Summary 14 Days Prior to Death:

The patient continued on oral etoposide at home with support from the palliative care team. Three months later the patient died at home.

Labs:

No lab reports available within 2 weeks of death.

PRACTICE CASE #2

CASE SUMMARY	
Age at initial diagnosis:	1 day
Time from initial diagnosis to death:	5 days
Diagnosis:	Brain tumor
Last treatment protocol:	No treatment received
Duration of last treatment:	Not applicable
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Summary 14 Days Prior to Death:

This patient was born at full term to a mother with no significant past medical history. The patient's head circumference was above the 99th percentile and the patient demonstrated neurological abnormalities. An MRI demonstrated presence of a brain tumor. The patient's parents were informed that cure was not possible, and supportive care only was implemented. The patient died in hospital 5 days following diagnosis with a do-not-resuscitate order in place.

Labs:

	14 Days Prior to Death
WBC	Normal
Absolute Neutrophil Count	Normal
Conjugated bilirubin	Normal
Ammonium	Normal
INR	Normal
Creatinine	Normal

PRACTICE CASE #3

CASE SUMMARY	
Age at initial diagnosis:	5 years
Time from initial diagnosis to death:	2 years
Diagnosis:	Brain tumor
Last treatment protocol:	Vinblastine
Time between last treatment and death	2 weeks
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

This patient was diagnosed with a brain tumor. Initial treatment consisted of partial resection followed by weekly vinblastine. There was no evidence of active disease until surveillance MRI demonstrated tumor progression and new spinal metastases. The family accepted the medical recommendation to withdraw curative treatment and initiate palliative radiation.

Treatment Summary 14 days Prior to Death:

No chemotherapy was prescribed. The patent received outpatient radiation to the brain and spinal cord over several days and a do-not-resuscitate order was placed on the chart. A few days following completion of radiation treatment, the patient died at home.

Labs:

No lab reports available within 2 weeks of death.

PRACTICE CASE #4

CASE SUMMARY	
Age at initial diagnosis:	3 years
Time from initial diagnosis to death:	12 years
Diagnosis:	Acute myeloid leukemia
Last treatment protocol:	UK MRC-10
Time between last treatment and death:	11.5 years
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

This patient was diagnosed with acute myeloid leukemia at 3 years of age and was treated according to UK MRC-10 with 4 cycles of chemotherapy without HSCT. The patient completed treatment and continued to demonstrate no evidence of disease at routine follow-up appointments for the next 11.5 years.

Treatment Summary 14 days Prior to Death:

At age 15, the patient was struck by a car while crossing the street. The patient was pronounced dead at the scene.

Labs:

No lab reports available within 2 weeks of death.

PRACTICE CASE #5

CASE SUMMARY	
Age at initial diagnosis:	12 years
Time from initial diagnosis to death:	5 years
Diagnosis:	Osteosarcoma
Last treatment protocol:	Etoposide
Time between last treatment and death:	2 days
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment background:

This patient was diagnosed with localized osteosarcoma of the humerus and was treated according to AOST 0331. The patient underwent a complete resection and completed chemotherapy uneventfully. The patient remained disease free until experiencing a relapse 3 years later. Multiple salvage regimens were attempted including available phase 1 trials. However the disease was refractory to all treatments. A CT scan 1 month prior to death demonstrated diffuse lung metastases. The patient was admitted to the hospital for symptom control and oral etoposide was prescribed as palliative intent chemotherapy.

Treatment summary 14 days prior to death:

The patient remained on oral etoposide until 2 days prior to death. In the 14 days prior to death, the patient developed increasing respiratory distress. The etoposide was discontinued and a morphine infusion was started. The patient died in hospital with a do-not-resuscitate order in place.

Labs:

	14 Days Prior to Death
WBC	Below lower limit of normal
Absolute Neutrophil Count	Below lower limit of normal
Conjugated bilirubin	Normal
Ammonium	Normal
INR	Normal
Creatinine	Normal

PRACTICE CASE #6

CASE SUMMARY	
Age at initial diagnosis:	8 years
Time from initial diagnosis to death:	1 day
Diagnosis:	Astrocytoma
Last treatment protocol:	N/A
Time between last treatment and death	N/A
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Summary 14 days Prior to Death:

This previously healthy patient presented to the emergency department with complaints of headache and visual disturbance. On CT, the patient was noted to have a large intracranial lesion that was later confirmed on MRI. The patient demonstrated high intracranial pressure (ICP) on imaging and an external ventricular drain (EVD) was placed. The patient was scheduled for brain tumor biopsy later that day, and treatment according to ACNS 0432 was planned following surgery. During the surgery, seeding of the tumor was noted throughout and follow-up MRI demonstrated diffuse leptomeningeal involvement. Surgery was uneventful and the patient was responding well to verbal commands the next morning during recovery in the ICU. However, later in the day the patient experienced high ICP despite continuous drainage of large amounts of cerebrospinal fluid from the EVD. The patient became hypertensive, developed progressive acute respiratory distress and was intubated. An emergency MRI demonstrated massive bleeding at the biopsy site and herniation. The patient became unresponsive and pupils were noted to be fixed and dilated. Despite maximum resuscitation efforts, the patient succumbed shortly thereafter.

Labs:

	14 Days Prior to Death
WBC	> 2 times upper limit of normal
Absolute Neutrophil Count	> 3 times upper limit of normal
Conjugated bilirubin	Normal
Ammonium	Normal
INR	Normal
Creatinine	Normal

PRACTICE CASE #7

CASE SUMMARY	
Age at initial diagnosis:	4 years
Time from initial diagnosis to death:	4 years
Diagnosis:	Acute myeloid leukemia
Last treatment protocol:	FLAG
Time between last treatment and death	3 months
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

This patient was diagnosed with acute myeloid leukemia at 4 years of age and was treated according to POG 9421. The patient completed treatment and remained disease free until 3 years later when relapse was confirmed. The patient then underwent treatment with FLAG. Bone marrow aspiration following two cycles of FLAG showed 6% myeloblasts at which time the patient proceeded to HSCT. Conditioning for the transplant was started 3 months prior to the patient's death. Following the transplant the patient experienced several complications including hypertension, febrile neutropenia, nausea and vomiting, diarrhea and hepatomegaly. In spite of prophylaxis for GVHD, the patient developed grade 3 gut and skin GVHD. High dose steroid therapy and immunosuppression were not effective and prior to death, the patient experienced worsening bloody stools and increasing respiratory distress.

Treatment Summary 14 days Prior to Death:

The patient was intubated in the ICU. CT scan showed multiple well-defined opacities and BAL showed *Aspergillus*. The gut GVHD continued to worsen in spite of maximal medical therapies. Multi-organ dysfunction developed with renal failure and hepatic failure combined with increasing jaundice. Continuous veno-venous hemofiltration was initiated. Due to the patient's poor prognosis, palliative care was recommended and supportive therapy was withdrawn. The patient died shortly thereafter.

Labs:

	14 Days Prior to Death
WBC	Normal
Absolute Neutrophil Count	Normal
Conjugated bilirubin	> 10 times upper limit of normal
Ammonium	> 2.5 times upper limit of normal
INR	> 2.5 times upper limit of normal
Creatinine	Normal

PRACTICE CASE #8

CASE SUMMARY	
Age at initial diagnosis:	3 years
Time from initial diagnosis to death:	1 year
Diagnosis:	Acute lymphoblastic leukemia
Last treatment protocol:	BFM-REZ
Time between last treatment and death:	2 months
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

This patient was diagnosed with acute lymphoblastic leukemia and was treated according to AALL 0232. After induction chemotherapy, remission was not attained and thus, the patient underwent an unrelated donor allogeneic stem cell transplantation. Following transplant the patient remained disease free until a bone marrow aspiration confirmed relapse 1 year later. The patient was admitted to hospital for treatment with BFM-REZ chemotherapy. Following cycle 1, the patient's counts did not recover, and the patient developed fever, cough and increased work of breathing. CT showed multiple pulmonary nodules. Mucor was confirmed on lung biopsy and the patient was treated with anti-fungal therapy. Chemotherapy was placed on hold.

Treatment Summary 14 days Prior to Death:

The patient continued to demonstrate work of breathing which progressed to respiratory failure. The patient was transferred to the intensive care unit where CPAP was initiated. Two weeks prior to death, peripheral blood demonstrated increasing blasts and thus, future chemotherapy was documented as being futile. The patient was transitioned to palliative care and died shortly after withdrawal of therapy.

Labs:

	14 Days Prior to Death
WBC	> 5 times upper limit of normal, peripheral blasts present
Absolute Neutrophil Count	Normal
Conjugated bilirubin	Normal
Ammonium	Normal
INR	Normal
Creatinine	Normal

PRACTICE CASE #9

CASE SUMMARY	
Age at initial diagnosis:	12 years
Time from initial diagnosis to death:	2 days
Diagnosis:	Acute promyelocytic leukemia
Last treatment protocol:	None
Time between last treatment and death:	N/A
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment summary 14 days prior to death:

This previously healthy patient presented to the emergency department with reports of fatigue, headache and extensive bruising. Initial bloodwork demonstrated the presence of blasts with extensive Auer rods. The patient was diagnosed with acute promyelocytic leukemia and admitted for chemotherapy. Prior to chemotherapy or ATRA initiation, the patient experienced a 10 minute seizure and had decreased level of consciousness. Clinical notes documented a left sided stroke. Brain MRI demonstrated extensive acute infarct with hemorrhage and the patient was transferred to the intensive care unit. The patient received blood product support for disseminated intravascular coagulation. ATRA and idarubicin were planned but before they could be started, physical examination revealed bilateral fixed dilated pupils and cerebral herniation was confirmed on CT. Withdrawal of support was recommended and death occurred soon after support withdrawal.

Labs:

	14 Days Prior to Death
WBC	> 4 times upper limit of normal, peripheral blasts present
Absolute Neutrophil Count	Normal
Conjugated bilirubin	Normal
Ammonium	Normal
INR	> 2.5 times upper limit of normal
Creatinine	Normal

PRACTICE CASE #10

CASE SUMMARY	
Age at initial diagnosis:	10 years
Time from initial diagnosis to death:	3 months
Diagnosis:	Acute myeloid leukemia
Last treatment protocol:	UK MRC-10
Time between last treatment and death:	2 weeks
TRM DESIGNATION	☐ **PD** or ☐ **TRM**

Treatment Background:

This patient was diagnosed with M5 AML and was CNS negative. Treatment according to UK MRC-10 was initiated and the patient completed the first two cycles uneventfully with the exception of uncomplicated fever and neutropenia. Bone marrow aspiration confirmed remission following completion of Induction 1. The patient received Intensification 1 and was discharged home with plans to return to clinic for follow-up.

Treatment Summary 14 days Prior to Death:

One week following hospital discharge, the patient presented to the emergency room with fever and septic shock. Resuscitation included intubation, vasopressor support and broad spectrum antibiotic therapy. Blood cultures grew viridans group streptococci from both the peripheral and central cultures. The patient developed severe coagulopathy and progressive acute respiratory distress syndrome requiring high frequency oscillation. Hemodialysis was initiated because of acute renal failure. In spite of maximal supportive care, cardiac arrest occurred and all resuscitation efforts were unsuccessful.

Labs:

	14 Days Prior to Death
WBC	Below lower limit of normal, peripheral blasts absent
Absolute Neutrophil Count	Below lower limit of normal
Conjugated bilirubin	Normal
Ammonium	Normal
INR	> 1.5 times upper limit of normal
Creatinine	> 1.5 times upper limit of normal

Appendix 3. Practice Cases: Answer Key

Case #	Designation	Flow Chart	Cause-of-Death Attributions*
1	**PD**	**#5:** Clinician specified "progressive disease" **OR** current cancer therapy has no curative intent (with associated key words) = YES	-
2	**PD**	**#5:** Clinician specified "progressive disease" **OR** current cancer therapy has no curative intent (with associated key words) = YES	-
3	**PD**	**#5:** Clinician specified "progressive disease" **OR** current cancer therapy has no curative intent (with associated key words) = YES	-
4	**TRM**	**#1:** Patient in remission = YES	**1) External Causes (Probable)** • *Unintentional injury*
5	**PD**	**#5:** Clinician specified "progressive disease" **OR** current cancer therapy has no curative intent (with associated key words) = YES	-
6	**TRM**	**#4:** Too unstable at presentation **OR** had treatment planned but died prior to receipt = YES	**1) Hemorrhage (Probable)** • *Acute symptomatic intracranial hemorrhage* **2) Nervous System (Probable)** • *Acute symptomatic hemorrhage or stroke* • *Acute symptomatic raised intracranial pressure* **3) Respiratory System (Probable)** • *Acute symptomatic respiratory distress leading to intubation*
7	**TRM**	**#5:** Clinician specified "progressive disease" **OR** current cancer therapy has no curative intent (with associated key words) = NO	**1) Infections (Probable)** • *Clinically documented infection with associated microbiologically documented organism* **2) Immune Mediated (Probable)** • *Worsening symptomatic GVHD*

			3) Respiratory System (Probable) • *Acute symptomatic respiratory distress leading to intubation* **4) GI System (Probable)** • *Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin > 10x ULN or high ammonium > 2.5x ULN or INR > 2.5x ULN* **5) Renal System (Probable)** • *Acute kidney injury with renal replacement therapy received*
8	**PD**	**#5:** Clinician specified "progressive disease" **OR** current cancer therapy has no curative intent (with associated key words) = YES	**-**
9	**TRM**	**#4:** Too unstable at presentation **OR** had treatment planned but died prior to receipt = YES	**1) Hemorrhage (Probable)** • *Acute symptomatic intracranial hemorrhage demonstrated by imaging* **2) Nervous System (Probable)** • *Acute symptomatic hemorrhage or stroke demonstrated by imaging* **3) Nervous System (Possible)** • *Seizure lasting 5 - <30 minutes within 48 hours of death*
10	**TRM**	**#1:** Patient in remission = YES	**1) Infections (Probable)** • *Clinically documented infection with associated microbiologically documented organism* **2) Respiratory System (Probable)** • *Acute symptomatic respiratory distress leading to intubation* **3) Renal System (Probable)** • *Acute kidney injury with dialysis received*

*Reminder: cause-of-death attributions are for TRM-designated cases only
Abbreviations: GVHD = graft-versus-host disease; INR = international normalized ratio; PD = progressive disease; TRM = treatment-related mortality; ULN = upper limit of normal