## THERAPY INTENSITY LEVEL

**TILBasic = TIL Basic**

<table>
<thead>
<tr>
<th>1. CDE Variable</th>
<th>TILBasic = TIL Basic; Global summary measure of Therapy Intensity Level for control of Intracranial Pressure (ICP).</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. CDE Definition</td>
<td>This summary measure captures a global categorization of therapy intensity over a given period. This may be assessed on a daily basis, or represent a single summary measure over the entire ICU period.</td>
</tr>
<tr>
<td>3. Recommended instrument for assessment</td>
<td>Chart review by investigator or trained research assistant.</td>
</tr>
<tr>
<td>4. Description of measure</td>
<td>Categorical measure; unique entry</td>
</tr>
</tbody>
</table>
| 5. Permissible values | **TIL 0**: No specific ICP directed therapy  
**TIL 1 – basic ICU care**  
- Sedation for ventilator/endotracheal tube tolerance  
- Volume/vasopressors for non-CNS cause (e.g. sepsis, myocardial injury)  
- Head up positioning (ventilator bundle)  
- Normocapnia (PaCO2 ≥ 40mmHg)  
**TIL 2 – Mild**  
- Higher levels of sedation  
- Vasopressors/volume for CPP support  
- Low dose osmotic therapy  
- Mild hypocapnia (PaCO2 4.6-5.3 kPa; 35-40 mmHg)  
- CSF drainage < 120 ml/day (<5 ml/hour)  
**TIL 3 – Moderate**  
- Higher doses of osmotic therapy  
- Moderate hypocapnia (PaCO2 4.0-4.5 kPa; 30-35 mmHg)  
- Mild hypothermia (> 35°C)  
- CSF drainage ≥ 120 ml/day (>5 ml/hour)  
**TIL 4 – Extreme**  
- Profound hypocapnia (PaCO2 < 4.0 kPa; < 30 mmHg)  
- Hypothermia < 35°C  
- Metabolic suppression for control of ICP  
- Surgery for refractory ICP (decompression, lobectomy) |
| 6. Classification: Basic/Intermediate/Advanced | Basic |
| 7. Procedure | A judgement of the basic TIL for a given period should be recorded by the investigator or a trained research assistant and entered as a single data entry for that period. |
8. Comments/Special instructions:
Interpretation of data on intracranial pressure is difficult without some reference to the intensity of therapy directed at control of ICP. Therapy Intensity Level can be documented in great detail. The aim of the basic-TIL classification scheme is to broadly categorize treatments into different levels.

**Level 0:** no specific ICP directed therapy

**Level 1:** this category includes any intervention required for general ICU care. This can include sedation. The dose of sedation is not specified, since sedation requirements and specific drug use are known to vary between centers and patients; the requirement is that sedative use in this category is not targeted to control ICP. Similarly, the use of vasoactive drugs (e.g. for sepsis) may vary between centers, but at this level they would not be used to support CPP. The underlying implication is that ICP and compliance are **not** a concern in this group of patients.

**Level 2:** this category includes interventions that are relatively modest – the key issue is that they are targeted to ICP/CPP control. The implication is that ICP and pressure volume relation **are** a concern in this group. Thus, with sedation, dose and drugs may vary but the intention is that they are being used to modulate ICP. Similarly, this category would include the use of vasoactive agents, which are being used to support a CPP target. The use of osmotic agents is included in this category, but only for the control of moderate or transcient elevations of ICP, that respond readily to therapy. Arbitrarily, a threshold over a 24 hour period could be set at 2 gr/kg Mannitol or 0.3 gr/kg Hypertonic saline. For estimating the intensity of hyperosmolar therapy, the total osmolar load of all agents given should be taken into consideration.

**Level 3:** this level includes most patients who have major problems with ICP/CPP management, but in common clinical practice, are not 'refractory' to common therapies.

**Level 4:** this level includes therapies that are used in patients with refractory intracranial hypertension. Allocating the use of sedative agents to this level requires that the agent (typically pentobarbital or thiopental, but sometimes propofol, etomide or other agents) is being used with the aim of substantially reducing cerebral oxygen utilization, often with monitoring of brain electrical activity and titration of sedation to burst suppression. Surgery for refractory ICP and hypothermia < 35 °C would always warrant classification at level 4.

**Note:** The TIL Basic only provides a broad, but nevertheless highly relevant, categorization of therapy intensity. It is simple to assess, but a drawback is that it is inherently flawed by subjectivity and regional variations in opinions about what constitutes a more or less intense therapy. For example, CSF drainage is seen as an early intervention in centers who monitor ICP by means of ventriculostomy, but will constitute a later invention in centers where parenchymal probes are routinely used for ICP monitoring.

The more detailed summary TIL as presented in the intermediate/advanced modules can be collapsed into an approximation of the TIL Basic, according to the following conversion table:

<table>
<thead>
<tr>
<th>TIL Basic</th>
<th>Summary score full TIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIL 1</td>
<td>0-3</td>
</tr>
<tr>
<td>TIL 2</td>
<td>4-6</td>
</tr>
<tr>
<td>TIL 3</td>
<td>8-10</td>
</tr>
<tr>
<td>TIL 4</td>
<td>≥ 11</td>
</tr>
</tbody>
</table>

This proposal for conversion/collapsing the full summary TIL into the TIL basic constitutes no more than expert opinion recommendations of the working group and should be subjected to field testing prior to any uncritical use.

9. Rationale/justification:
ICP is often regarded as a surrogate endpoint in TBI and considered a surrogate for the
intensity of a range of pathophysiological processes. Interpretation of ICP is however not possible without knowledge of the intensity of therapy directed at ICP/CPP control. Modern, neuro-ICU practices have substantially blunted our ability to use ICP as a surrogate marker. It is possible to control ICP by intensifying ICP/CPP therapies, until the system terminally decompensates and intracranial hypertension becomes refractory to therapy. In this context, the intensity of ICP/CPP targeted therapy may be a more sensitive measure of the severity of pathophysiology, and the ability of a novel intervention to modify such pathophysiology.

10. References:
## THERAPY INTENSITY LEVEL

### TILDif = TIL Differentiated

1. **CDE Variable**
   
   TILDif = TIL Differentiated for various treatment modalities aimed at prevention or control of raised Intracranial Pressure (ICP) and/or for CPP management.

2. **CDE Definition**
   
   TIL is assessed separately for the following treatment modalities:
   - Position
   - Sedation/metabolic suppression and neuromuscular blockade
   - CSF drainage
   - Fluid loading and vasopressor therapy
   - Hyperventilation
   - Hyperosmolar therapy
   - Treatment of fever and hypothermia
   - Surgery for refractory ICP (decompression/lobectomy)

3. **Recommended instrument for assessment**
   
   Chart review by investigator or trained research assistant.

4. **Description of measure**
   
   Categorical measure

5. **Permissible values**

   **Position**
   - Head elevation for ICP control
   - Nursed flat 180º for CPP management

   **Sedation/metabolic suppression and neuromuscular blockade**
   - Sedation (low dose as required for mechanical ventilation)
   - Higher dose sedation for ICP control (not aiming for burst suppression)
   - Metabolic suppression for ICP control with high dose barbiturates, propofol, ethomydate or other agents
   - Neuromuscular blockade (paralysis)

   **CSF drainage**
   - < 120 ml/day (<5 ml/hour)
   - CSF drainage at ≥ 120 ml (≥ 5 ml/hour)

   **Fluid loading and vasopressor therapy**
   - Fluid loading for maintenance of cerebral perfusion
   - Vasopressor therapy required for management of cerebral perfusion

   **Hyperventilation**
   - Mild hypocapnia for ICP control (PaCO2 4.6-5.3 kPa; 35-40 mmHg)
   - Moderate hypocapnia for ICP control (PaCO2 4.0-4.5 kPa; 30-34 mmHg)
   - Intensive hypocapnia for ICP control (PaCO2 < 4 kPa; 30 mmHg)

   **Hyperosmolar therapy**
- Hyperosmolar therapy with mannitol (≤ 2 gr/kg/24 hours)
- Hyperosmolar therapy with hypertonic saline (< 0.3 gr/kg/24 hours)
- Hyperosmolar therapy with mannitol in doses > 2/gr/kg/24 hours
- Hyperosmolar therapy with hypertonic saline in doses > 0.3/gr/kg/24 hours

**Treatment of fever and hypothermia**
- Treatment of fever (temp > 38 °C) or spontaneous temp below 34.5 °C
- Mild hypothermia for ICP control with a lower limit of 35 °C
- Hypothermia below 35 °C

**Surgery for refractory ICP (decompression/lobectomy)**
- Intracranial operation for progressive mass lesion, not scheduled on admission
- Decompressive craniectomy

All categories for the differentiated Therapy Intensity Level are presented in the TILDif module, and should be answered by ‘no/yes’.
The advanced version includes detailed recording of fluids, dose of vasopressors and hyperosmolar agents, administered over the given 24 hour period.
**Fluids in:** crystalloids/colloids in ml.
**Blood and derivatives** in ml.
**Fluid out:** in ml
**Vasopressors:** noradrenaline/phenylephrine/dopamine in mg.
**Hyperosmolar agents:** mannitol/Hypertonic saline in gr.

### 6. Classification:
**Basic/Intermediate/Advanced**
- Intermediate/advanced
- Advanced version: recordings of fluid balance, vasopressors and hyperosmolar agents.

### 7. Procedure
Obtain information on TIL differentiated for therapy intensity from medical chart and/or PDMS review.
Documenting the TIL differentiated is recommended on a daily basis.
Threshold levels for hyperventilation should be obtained from arterial blood gas analysis. Expired CO2 levels are not an acceptable alternative.

### 8. Comments/Special instructions:
**Position**: mark ‘yes’ if the patient was nursed with head elevation for ICP control or nursed flat 180° for CPP management. As both positions are mutually exclusive, but may be employed consecutively, we recommend to only mark the position employed for the greatest part of the time period over which the TIL is assessed.

**Sedation and metabolic suppression**: no individual drug or dose is specified as the aim is to match the intervention severity to the difficulty in controlling ICP. Sedation TIL is therefore critically dependent on the aim of sedation, irrespective of drug or dosage use.

**Hyperventilation**: only use arterial blood gas analysis for determining level of hyperventilation. Inadvertent hypocapnia should not be scored as a higher TIL, unless
infracranial hypertension is a clinical problem. The aim is to record hypocapnia levels employed for control of ICP.

**Hyperosmolar therapy:** the osmotic effect depends on the excess osmolar load, and hence the concentration administered (particularly a problem with hypertonic saline which is used in different concentrations). The threshold levels used are broadly equivalent in osmotic load (2 gr mannitol = 0.3 gr NaCl = 11 mOsm). Caution is advised when using mannitol in combination with hypertonic saline.

**Surgery for refractory ICP:** evacuation of an infracranial space occupying lesion planned at admission, does not qualify as a marker of TIL. The score should reflect surgical interventions required exclusively (and usually secondarily) for ICP control. Only mark ‘infracranial operation for progressive mass lesion’ on the day that this was performed. If decompressive craniectomy is/was performed, please mark this on the day of surgery and also for all successive days.

Recording of TIL can be performed even when ICP is not monitored. However guidelines strongly recommend the use of ICP monitoring when therapy is employed for ICP control or CPP management.

**Note:** thresholds used are based on consensus, and may need review with emerging evidence.

9. **Rationale/justification:**
Interpretation of ICP is not possible without knowledge on the level of therapy intensity employed for ICP control and/or for CPP management. TIL can be recorded in great detail and has commonly been performed on an hourly basis. Such detailed recording however, is resource intensive. Further, ICU practices have changed with most high grade interventions (such as metabolic suppression and temperature manipulation) now being used in a continuous fashion over periods of days or at least a large fraction of a day. Other discrete interventions (such as surgical decompression) happen as a single threshold event rather than as a repeated treatment. Given this context, the use of hourly recording of therapy intensity may be less relevant and the working group has doubts as to whether the data provided by hourly recording of TIL justifies the investment in time, particularly in the context of an increased (and probably increasing) burden of data collection in other areas (such as imaging and biomarkers). We therefore propose recording the therapy intensity level on a daily basis, under the presumption that this will offer a transparent and useful approach with the benefit of a lower burden than when hourly recording is performed. The relative benefits of this recommendation and validation/updating of the threshold levels chosen, require further testing in the clinical situation. The specified treatment modalities and categories are compatible with the pediatric TIL proposed by Shore et al.

10. **References:**


# THERAPY INTENSITY LEVEL

## TILSum = Summary TIL

<table>
<thead>
<tr>
<th>1. CDE Variable</th>
<th>TILSum = Summary TIL quantifies the total level of therapy intensity over a given period and is derived from the differentiated TIL presented in the template 'TILDif'.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. CDE Definition</td>
<td>Quantification of total therapy intensity for control of ICP and/or CPP management by attributing numerical values to each modality of the differentiated TIL and summatting these values to a summary score.</td>
</tr>
<tr>
<td>3. Recommended instrument for assessment</td>
<td>Summary score</td>
</tr>
<tr>
<td>4. Description of measure</td>
<td>Numerical scale</td>
</tr>
</tbody>
</table>
| 5. Permissible values | **Summary score:**
|                          | 0-38  
|                          | Calculating summary TIL: see below. |
| 7. Procedure | The summary TIL is not assessed bedside but can be calculated from the TIL differentiated as described below. This can be an automated procedure, or manually performed by the investigator or trained research personnel. The summary TIL can be calculated on a daily basis or, for example, over the entire ICU period. A daily calculation is recommended. |

### 8. Comments/Special instructions:
The aim of the summary TIL is to produce a quantitative estimate of the interventions used in any given period (recommended 24 hours) by assigning numerical scores to each therapy intensity level of each intervention and summatting these. This has successfully been done for pediatric TBI (Shore et al 2006). The treatment modalities assessed in the summary TIL and the scores assigned are largely compatible with the pediatric TIL. For both scales the maximum score is 38. The summary TIL thus provides opportunities for comparing therapy intensity between pediatric and adult populations. The summary TIL provides a refinement in the quantification in the assessment of therapy intensity, but it is essential that we take account of a few caveats. First, the allocation of intensity scores to individual levels of each intervention is arbitrary, and based on custom and clinical judgement. Thus, there is no empirical basis for declaring that for example metabolic suppression with intravenous anaesthetics should score 4 times as high as simple sedation, twice as high as neuromuscular blockade, or the same level as decompressive craniectomy. Second, these scores are arbitrary, non-parametric and intervention-specific ordinal metrics. The summary score will not be normally distributed. Consequently, there needs to be a clear understanding of how summary data from such scoring is analysed. Parametric summary and inferential statistics are clearly inappropriate. It may be that the most useful application of the summary TIL will be to arrive at a consensus regarding broadly similar levels of intensity across interventions, thus accommodating local variations in practice. In effect, the process would establish an exchange rate for the different currencies of individual interventions. Indeed, this may be best conceptualized as a more objective and detailed method of arriving at a broad categorization as presented in the TIL Basic. An orienting
A proposal for conversion of the summary TIL into the TIL basic is presented in the template on TIL basic. This approach requires validation and most likely also amendment in clinical studies.

We see clear advantages in the use of the summary TIL and despite the fact that it has not yet been clinically validated, recommend it for use in patients with severe TBI. A great advantage of this method is that it allows a communality of approach across ages, being applicable both in pediatric and adult populations. Validation of the summary score in clinical studies is required prior to an uncritical use in clinical studies.

9. Rationale/justification:

10. References:
## CALCULATING SUMMARY TIL

<table>
<thead>
<tr>
<th>Assignment of scores to correspond with PED version</th>
<th>Score</th>
<th>Max score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head elevation for ICP control</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nursed flat (180°) for CPP management</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sedation (low dose as required for mechanical ventilation)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Higher dose sedation for ICP control (not aiming for burst suppression)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Metabolic suppression for ICP control with high dose barbiturates or propofol</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Neuromuscular blockade (paralysis)</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>CSF drainage &lt;120 ml/day (&lt;5 ml/hour)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CSF drainage ≥ 120 ml/day (≥ 5 ml/hour)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fluid loading for maintenance of cerebral perfusion</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vasopressor therapy required for management of cerebral perfusion</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mild hypocapnia for ICP control [PaCO2 4.6-5.3 kPa (35-40 mmHg)]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderate hypocapnia for ICP control [PaCO2 4.0-4.5 kPa (30-35 mmHg)]</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Intensive hypocapnia for ICP control (PaCO2 &lt; 4 kPa (30 mmHg))</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hyperosmolar therapy with mannitol up to 2 g/kg/24 hours</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar therapy with hypertonic saline up to 0.3 g/kg/24 hours</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar therapy with mannitol &gt; 2 g/kg/24 hours</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar therapy with hypertonic saline &gt; 0.3 g/kg/24 hours</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Treatment of fever (temp &gt; 38°C or spontaneous temp &lt; 34.5°C)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mild hypothermia for ICP control with a lower limit of 35°C</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hypothermia below 35°C</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Intracranial operation for progressive mass lesion, not scheduled on admission</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decompressive craniectomy</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

Total maximal score: **38**