DATA DICTIONARY

And

CASE REPORT FORM INSTRUCTIONS

For

Bacteremia **A**ntibiotic **L**ength **A**ctually **N**eeded for **C**linical **E**ffectiveness (**BALANCE**): A Randomized Controlled Clinical Trial

NOTE: data dictionary and definitions are same for ICU and Non-ICU patients except that separate CRF with non_ICU specific variables will be used for non-ICU patients.

ELIGIBILITY CRITERIA FORM 1.1

Study ID Format

Patient ID number is a 6 digit number made up of 2 parts.

- the first two digits identify study centre (site ID).
- The next 4 digits designate the patient's sequential randomization number within the center.

Randomized Patient Identification Number (randomization number):

- Identification number for randomized patients will be assigned by the computerized randomization system .These patients are designated as type "1", therefore the third digit will always be a "1" in their patient ID. The last three digits will increase sequentially up to 999 within any one Center.

Example:

- The first randomized patient at Center 1 would have a Patient ID Number = 01-1001.
- The 15^{th} randomized patient at Center 1 would have a Patient ID Number = 01-1015.

Eligibility Criteria:

- to be included, a patient must meet both inclusion criteria and none of the exclusion criteria

- patients will be identified from blood culture records in the microbiology laboratory, so site coordinators will need to obtain daily list of all patients with positive blood cultures obtained from patients in the intensive care unit.

- inclusion criteria:

    1. patient is in an ICU or non- ICU ward at the time the blood culture is drawn or reported as positive AND

    2. patient has a positive blood culture with pathogenic bacteria (refer to organism codes table).

- exclusion criteria:
    1. patient already enrolled in the trial.
    2. patient has severe immune system compromise, as defined by: absolute neutrophil count <0.5x109/L; or is receiving immunosuppressive treatment for solid organ or bone marrow or stem cell transplant
    3. Patient has a prosthetic valve or synthetic endovascular graft
    4. patient has documented or strong suspicion of syndrome with well-defined requirement for prolonged treatment:
        i) infective endocarditis
        ii) osteomyelitis/septic arthritis
        iii) undrainable/undrained abscess
        iv) unremovable/unremoved prosthetic-associated infection (e.g. infected pacemaker, prosthetic joint infection, ventriculo-peritoneal/pleural shunt infection etc.)
        (**note: central venous catheters, including tunneled central intravenous catheter, and urinary catheters are not excluded unless the treating clinical team does not have equipoise for enrollment and randomization to either group**)
    5. patient has a single positive blood culture with a common contaminant organism according to Clinical Laboratory & Standards Institute (CLSI) Guidelines:
        - Coagulase negative staphylococci
        - *Bacillus spp.(see the list of Aerobic spore forming bacillus below)*
        - *Corynebacterium spp.*
        - *Propionobacterium spp.*
        - *Aerococcus spp.*
        - *Micrococcus spp.*
    6. patient has a positive blood culture with Staphylococcus aureus or Staphylococcus lugdunensis.
    7. patient has a positive blood culture with Candida spp. or other fungal species.

Note:

- **if the blood culture is collected in the ICU and is reported as positive while patient is still in the ICU– enrol under ICU category of randomize.net.**

- **if the blood culture is collected in the ICU and is reported as positive while patient is in the non-ICU ward– enrol under ICU category of randomize.net.**

- **if the blood culture is collected on non-ICU wards and is reported as positive while patient is still in the non-ICU ward - enrol under BALANCE wards category of randomize.net.**

- **if the blood culture is collected on non-ICU wards and is reported as positive while patient is in the ICU - enrol under ICU category of randomize.net.**

- **For ICU ONLY sites: if an eligible patient is discharged from ICU to hospital ward before obtaining consent, please approach the ward treating team to seek permission for possible enrolment (within 7 days).**

Aerobic spore forming bacillus (generally excluded)

- *Aneurinibacillus aneurinilyticus Aneurinibacillus migulanus*
- *Aneurinibacillus thermoaerophilus*
- *Bacillus amyloliquefaciens*
- *Bacillus azotoformans*
- *Bacillus badius*
- *Bacillus brevis*
- *Bacillus carboniphilus*
- *Bacillus cascainensis*
- *Bacillus cereus*
- *Bacillus chitinolyticus*
- *Bacillus circulans*
- *Bacillus coagulans*
- *Bacillus edaphicus*
- *Bacillus ehimensis*
- *Bacillus endophyticus*
- *Bacillus fastidiosus*
- *Bacillus firmus*
- *Bacillus globisporus*
- *Bacillus halodurans*
- *Bacillus horti*
- *Bacillus kaustophilus*
- *Bacillus laterosporus*
- *Bacillus lentus*

- *Bacillus licheniformis*
- *Bacillus megaterium*
- *Bacillus mucilaginosus*
- *Bacillus naganoensis*
- *Bacillus niacin*
- *Bacillus oleronius*
- *Bacillus pallidus*
- *Bacillus pantothenticus*
- *Bacillus psychrophilus*
- *Bacillus psychrosaccharolyticus*
- *Bacillus pumilus*
- *Bacillus racemilacticus*
- *Bacillus silvestris*
- *Bacillus simplex*
- *Bacillus smithii*
- *Bacillus sphaericus*
- *Bacillus sporothermodurans*
- *Bacillus stearothermophilus*
- *Bacillus subtilis*
- *Bacillus thermocatenulatus*
- *Bacillus thermocloaceae*
- *Bacillus thermodenitriÆcans*
- *Bacillus thermoglucosidasius*
- *Brevibacillus agri*
- *Brevibacillus borstelensis*
- *Brevibacillus brevis*
- Brevibacillus centrosporus
- Brevibacillus choshinensis
- *Brevibacillus formosus*
- *Brevibacillus laterosporus*
- *Brevibacillus parabrevis*
- *Brevibacillus reuszeri*
- *Geobacillus kaustophilus*
- *Geobacillus stearothermophilus*
- *Geobacillus thermocatenulatus*

- *Geobacillus thermodenitriÆcans*
- *Geobacillus thermoglucosidasius*
- *Paenibacillus alginolyticus*
- *Paenibacillus alvei*
- *Paenibacillus amylolyticus*
- *Paenibacillus apiarius*
- *Paenibacillus azotoÆxans*
- *Paenibacillus borealis*
- *Paenibacillus chibensis*
- *Paenibacillus chondroitinus*
- *Paenibacillus curdlanolyticus*
- *Paenibacillus dendritiformis*
- *Paenibacillus glucanolyticus*
- *Paenibacillus illinoisensis*
- *Paenibacillus kobensis*
- *Paenibacillus koreensis*
- *Paenibacillus larvae*
- *Paenibacillus larvae*
- *Paenibacillus lautus*
- *Paenibacillus macerans*
- *Paenibacillus macquariensis*
- *Paenibacillus pabuli*
- *Paenibacillus peoriae*
- *Paenibacillus polymyxa*
- *Paenibacillus thiaminolyticus*
- *Paenibacillus validus*
- *Virgibacillus pantothenticus*
- *Virgibacillus proomii*

SCREENING FORM 1.2 (page 2 of 2)

- this form is to be filled for **ALL** patients who are Eligible but not randomized due to one of the following reasons:
    - patient or substitute decision maker (SDM) declined consent.
    - patient unable to give consent and SDM not available.
    - attending physician declined consent, reason: (please specify:_____)
    - consent not obtained due to other reason: (please specify:_____)

- patient status:
- if patient was randomized, please check the box for **Included** otherwise check the box for
- date of randomization:
    - please enter date when patient was randomized in dd/mm/yyyy format. Accurate date and time of randomization can be found in the email from randomization.net confirming enrollment.
    - sites not receiving randomization emails as per local date and time, please use the actual date and time of randomization if different than the one on randomize.net.

Randomization

The Randomization system for BALANCE will be through RANDOMIZE.NET (http://www.randomize.net/).

Patients can be enrolled up to day 7 of appropriate antibiotics, which in some cases will be different than day 7 from culture collection date.

Sites participating in hospital wide enrolment will have a separate account for ICU and non-ICU category for randomization on randomization.net.

RANDOMIZE.NET provides a comprehensive and secure randomization service for clinical trials which is run on the Internet. This system is used by many investigators due to the ease of use and tamper-proof methodology. This service allows for stratification by center and other variables. Steps for randomization are as follows:

1. On the day of positive blood culture result and after obtaining informed consent, the site research coordinator will login to http://www.randomize.net/ using (ICU or non-ICU) and follow the regular process of randomizing a subject. Please see separate step by step power point presentation on how to randomize a patient.

2. The final page will just indicate that the subject was successfully randomized. Treatment group designation will be concealed.

3. A confirmation email will be sent to the site research coordinator and to the coordinating center PIs and project manager indicating that the subject was randomized. No treatment arm will be shown in the email. This email will have the patient ID in sequence for the site.

4. After the full susceptibility results become available, the site research coordinator along with the site principal investigator will determine the date for day 7 (unblinding date) taking into account the cumulative number of days the patient already received adequate antibiotics between the blood culture collection date and the date the cultures were finalized, and the date the patient will complete 7 days of adequate antibiotics. This date will be entered into the randomize.net, so that the randomization email is sent to un-conceal the treatment designation on day 7 of adequate treatment.

5. Exactly on day 7 (date entered by the research coordinator), an email will be sent with the unblinded treatment for the subject. At this time the unblinded treatment for that subject will be displayed in the reports available to the site research coordinator. If a patient is randomized to the short (7 days) arm, the treating team will then be informed to stop the antibiotics; if the patient is randomized to the long (14 days) arm, the team will be informed to continue until day 14.

Calculating day 7 of adequate antibiotic is a complex procedure; there will be multiple different scenarios depending on how many adequate and inadequate antibiotic treatments were given prior to the cultures being finalized. The below diagram demonstrates some of these possible scenarios. Day 7 (unblinding date) will be calculated as the cumulative number of days the patient receives adequate antibiotics after the positive blood culture collection date; 'adequacy' will be determined based on the susceptibility reports for the pathogens when the results are finalized. If a patient received inadequate antibiotics after the positive blood culture collection and before the culture is finalized (scenario 3 below), day 7 date will be calculated from the date adequate antibiotic is started which should be immediately after the culture is finalized. If a patient received adequate antibiotic for one day after positive blood culture collection and then got switched to inadequate antibiotics until the culture was finalized (scenario 7 below), this one day of adequate antibiotic after positive culture collection will be counted in the calculation of the day 7 date. Once the culture is finalized, adequate antibiotic should be started/continued without any break until the completion of assigned treatment arm. Discontinuation or missed treatment before the completion of assigned treatment duration will be considered as a protocol violation, but will not alter the intended 'day 7' date.

Please use calendar days to calculate day 7. The easiest way of calculating day 7 (unblinding date) is to add 6 to the date of first appropriate dose receipt after positive culture, provided there was no interruption in appropriate treatment.

Similarly, day 14 (for 14 day arm) will be calculated by adding 13 to the date of first appropriate dose receipt after positive culture. Patients should receive a full day of appropriate antibiotics on the last day (e.g. all doses of appropriate antibiotics should be administered when the dosing schedule calls for more than one dose per day).

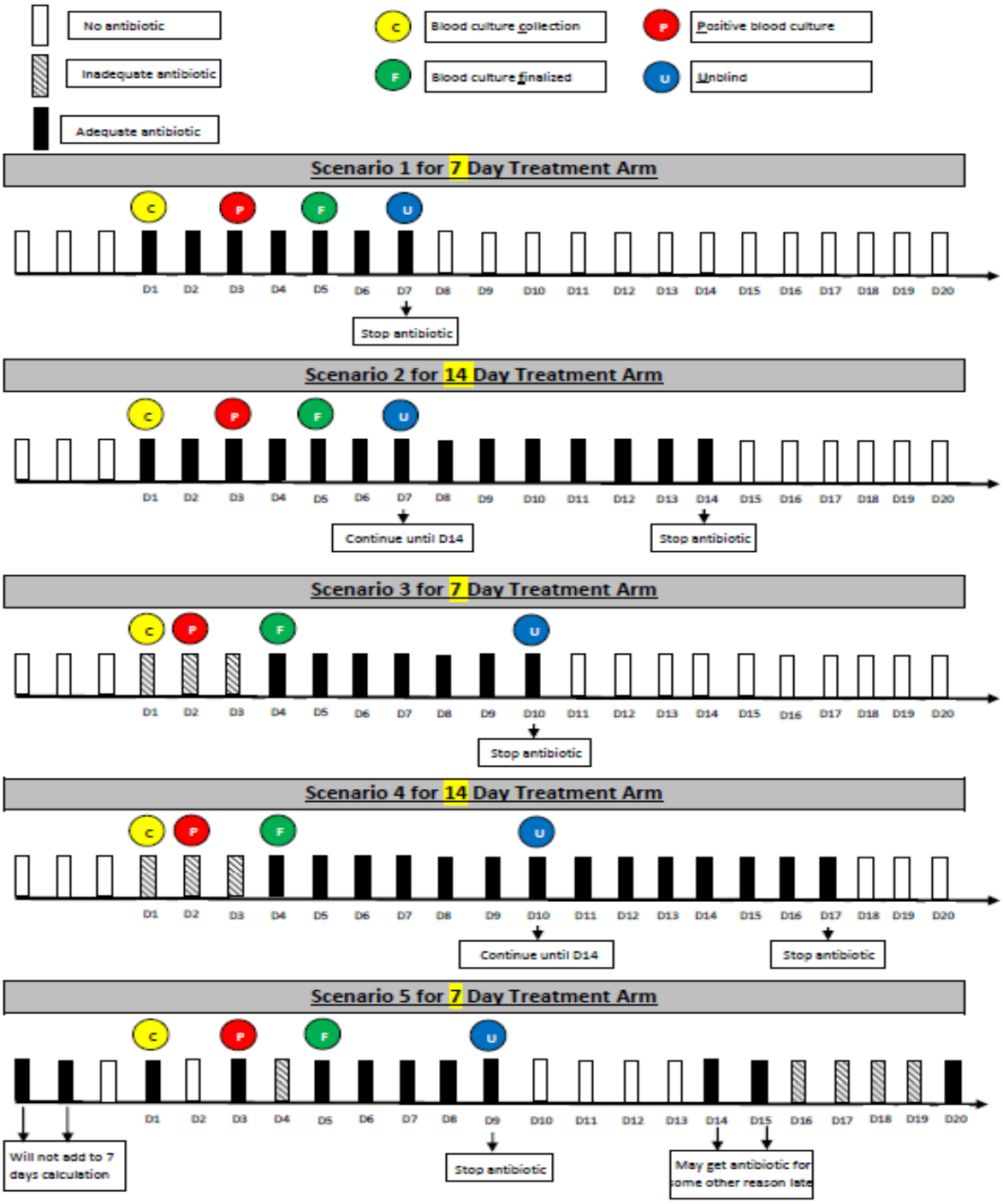
Example:

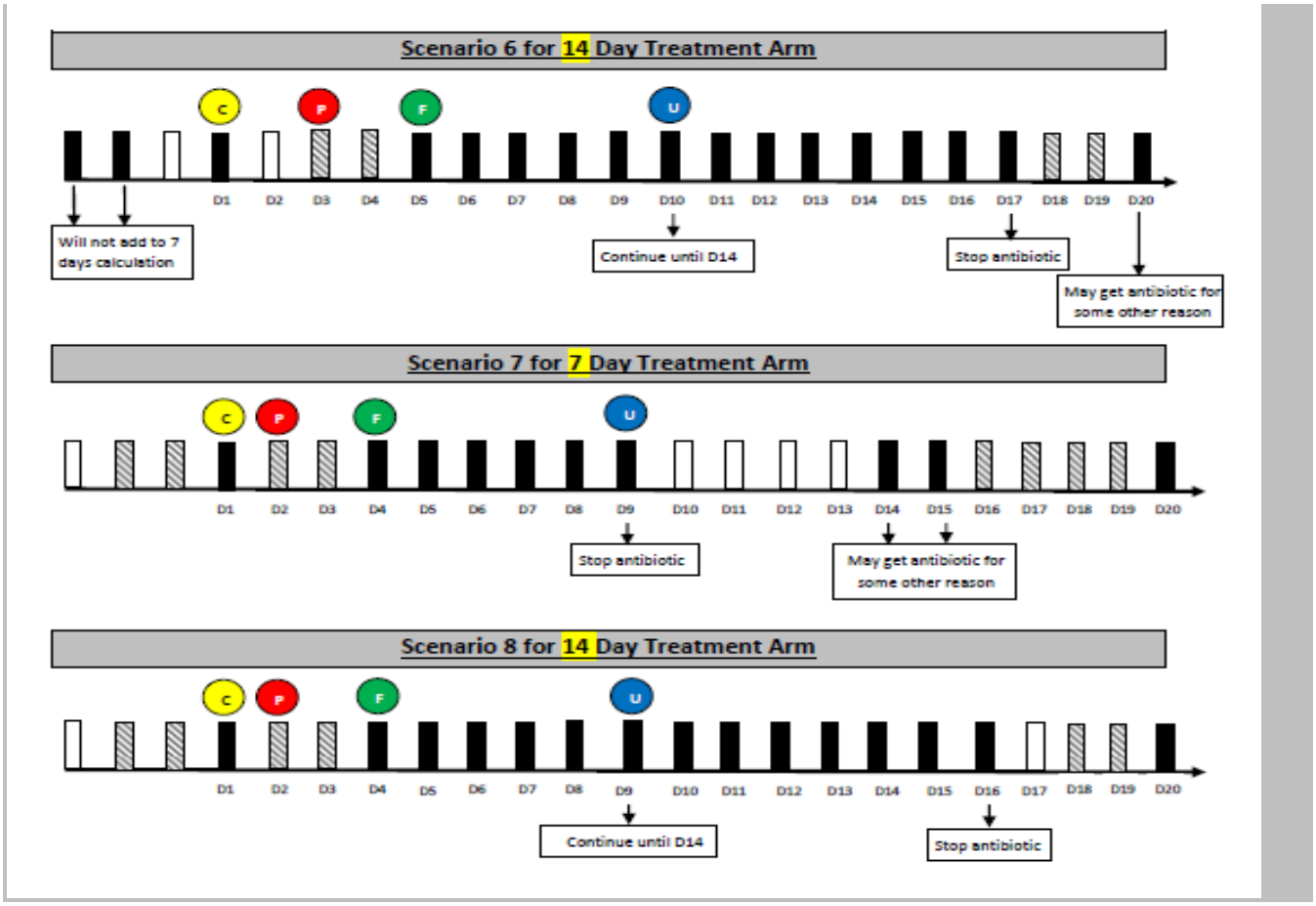
Date of positive blood culture= 01/12/2016 (December 01, 2016).

Date of first appropriate ABX= 02/12/2016 (December 02, 2016).

Day 7 (unblinding date) = (02nd + 6= 08) 08/12/2016 (December 08, 2016).

Day 14 (14 day group) = (02nd + 13= 15) 15/12/2016 (December 15, 2016).




Scenario 6 for 14 Day Treatment Arm
C
P
F
U
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14 D15 D16 D17 D18 D19 D20
Will not add to 7 days calculation
Continue until D14
Stop antibiotic
May get antibiotic for some other reason
Scenario 7 for 7 Day Treatment Arm
C
P
F
U
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14 D15 D16 D17 D18 D19 D20
Stop antibiotic
May get antibiotic for some other reason
Scenario 8 for 14 Day Treatment Arm
C
P
F
U
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14 D15 D16 D17 D18 D19 D20
Continue until D14
Stop antibiotic

DEMOGRAPHICS AND COMORBIDITIES FORM 2.1

- *if the patient has had more than one ICU admission, then the ICU admission date refers to the date of the current ICU admission during which the index positive blood culture was obtained (i.e. the positive blood culture that led to study enrolment).*

- APACHE II score:
  - can use value if already available from routine data collection in your ICU, assuming the standard operating procedures for its calculation are the same as we provide (CCCTG template).
  - otherwise please calculate the APACHE II score using the attached APACHE II standard operating procedure and worksheet which follow over next several pages.
  - note: the *APACHE II score will be calculated for the patient's first 24h in ICU* (not from the first 24h after positive blood culture).
  - APACHE II score will be calculated for all **Randomized** patients.

APACHE II Standard Operating Procedure (SOP) and Worksheet (derived from CCCTG template from the PROTECT study)

The APACHE prognostic scoring system was developed in 1981 at the George Washington University Medical Centre. It employs basic physiologic principles to stratify acutely ill adult patients by severity of illness. The basis for the development of this system was the hypothesis that the severity of acute disease, and therefore the risk of death, can be measured by quantifying the extent of the derangement in certain physiologic variables [1].

The APACHE II scoring system, is a simplified version of the original APACHE system, and consists of three sections: twelve acute physiologic variables, age, and chronic health status. The APACHE II score is determined by totalling points from these three sections, resulting in a total score between 0 and 71 points. Patients are assigned points based on the most deranged physiologic variables obtained on these assigned parameters during the patient's **initial 24 hours in an intensive care unit (ICU) setting**. Chronological age and severity of pre-existing chronic disease are also scored as they are thought to impact physiologic reserve and probability of survival during a period of acute illness [1].

One data point of the acute physiologic variables, the Glasgow Coma Score (GCS), has a large impact on the overall APACHE II score. The GCS demonstrates significant variability in its determination, affecting the overall APACHE II. It has the potential to contribute 17% of the theoretical maximum acute physiological score, which is more than any other variable in the APACHE II assessment [2]. Patients in the ICU receive large amounts of sedation and / or paralytic agents that can impair the accurate assessment of the GCS. For this reason, it is very important to collect GCS scores in the most accurate and consistent manner. Based on a prospective cohort study of 9848 patients from twenty-two general adult intensive care units, it is recommended that GCS be assessed directly (i.e. use the GCS score **prior to sedation**). This is more consistent compared to assuming GCS is normal in patients [2].

There are other data points that also have an impact when calculating an accurate APACHE II score. Assessment of pre-existing chronic disease, as well as assessing for acute renal failure, has an impact on the final total APACHE II score. The literature has suggested that adherence to consistent guidelines when

collecting this data decreases variability in final scores [1,2]. The following guidelines have been provided to you for your use in calculating APACHE II scores.

GENERAL INSTRUCTIONS

Worksheet Completion: *(Please refer to APACHE II worksheet which follows below)*

- Determine your 24-hour APACHE II assessment window. This time window is the patient's first 24 hours since being admitted to the ICU.
    - If they have transferred between multiple ICUs, then it is the 24h since being admitted to the first ICU).
- Follow the guidelines provided as you complete the APACHE II assessment.
- Proceed through the worksheet, completing each data point for physiologic variables, age points, and chronic health points. Check or fill in the circle that corresponds with the range for the value you have selected.
- To calculate the Total APACHE score, sum the 3 following domains:

A. PHYSIOLOGIC VARIABLES (APS) (total of **12** variables)

There will be 11 variables if there is no ABG available as the **oxygenation** and **Arterial pH variable** are not summated, however, you will be using the **Serum HCO_3** variable

- All APACHE II data collected must be from the first 24 hours following ICU admission. The GCS assessment should be taken prior to the patient receiving sedation. This may be outside of the 24-hour assessment period but will provide a more accurate score of neurological function.
- When recording variables for the Acute Physiology Score, if a physiologic measurement is not obtained during the 24 hour time frame, assign a zero ("0") point score.
- For all acute physiologic measurements: choose the *worst, most abnormal value* recorded during the full 24-hour assessment period. These values may be low or high, but will always be the most deranged value with the highest point score (furthest away from the column headed 0-Normal). Remember that this data is not compared to local laboratory values but rather the APACHE II scoring system.
- Do not include values from the Operating Room.
- Do not include values you assess as being transient (e.g. a 1 time spike or drop in blood pressure).

The 12 Physiological Variables are:

1. **Temperature**
    - Record rectal or core temperature in degrees Celsius (°C).

- Add 0.5°C if oral
- Add 1.0°C if axillary

2. **Mean Arterial Pressure (MAP)**
    - Record in mmHg
    - Use the following formula to calculate the MAP: SBP +[DBP×2]÷3
3. **Heart Rate**
    - http://translate.google.com/?hl=en&tab=TT. Do not score for bradycardia if a pacemaker is present.
    - Record the documented ventricular rate.
4. **Respiratory Rate**
    - Record the most deranged ventilated or non-ventilated rate.
5. **Oxygenation**
    - If the patient has a $FiO_2 < 0.5$ AND ≥ 0.5 within this same 24-hour period, use the $AaD0_2$ or PaO_2/FiO_2 value which scores highest in this category.
    - The formula to calculate $AaDO_2$ at sea level is: $[FiO_2 \times 713]-[PaCO_2 \div 0.8]- PaCO_2$
    - Please refer to your hospital laboratory for local barometric pressures because this impacts the value that should be used for accurate calculations. If you are at sea level (an altitude less than 1000 feet) use a barometric pressure of 760 mmHg minus the pressure of water (47 mmHg) for a total pressure of 713 mmHg.
    - Remember only 1 value should be accounted for in this oxygenation variable, Do not score for both PaO_2 and $AaDO_2$
6. **Arterial pH**
7. **Serum Sodium** (mmol/L)
8. **Serum Potassium** (mmol/L)
9. **Serum Creatinine** (mg/100mL or µmol/L)
    - Patients score double points for ACUTE renal failure.
10. **Hematocrit (%)**
11. **White Blood Cell Count** (total mm^3 in 1000s)
12. **Glasgow Coma Scale (GCS)**

- Calculate the GCS by assessing each of the three components: eye opening, motor response, and verbal response.
- Choose the most accurate, lowest cumulative score available in the 24-hour assessment period.
- If a patient has received sedation or paralytic agents, it is preferable to record the GCS prior to receiving the medications even if outside the 24-hour assessment period.
- If you are unable to obtain a reliable, pre-sedation GCS the neurological status should be scored as normal (GCS = 15).
- Patients who receive large amounts of sedation may have their GCS recorded as "3" (i.e. no response for eye opening, motor, or verbal). Unless there is a documented cause for the decreased level of consciousness (in addition to sedation) this should not be considered an accurate GCS.
- For intubated patients use your best clinical judgment when scoring "verbal response".
- For post-operative patients wait 6 hours to record the GCS if a patient has been admitted to the ICU from surgery

Enter the total score of the GCS based on the following definition:

Eye Opening Response	**Motor Response**	**Verbal Response**
Spontaneous = 4	Obeys Commands = 6	*If not intubated:*
To Voice = 3	Localizes to Pain = 5	Oriented = 5
To Pain = 2	Flexion / Withdrawal = 4	Confused = 4
None = 1	Abnormal Flexion = 3	Inappropriate = 3
	Extension = 2	Incomprehensible = 2
	No Response = 1	No Response = 1
		If intubated:
		Appears to be able to converse = 5
		Ability to converse questionable = 3
		Unresponsive = 1

Subtotal Eye	Subtotal Motor	Subtotal Verbal Total GCS =Subtotal (eye+motor+verbal) APACHE GCS Points = 15 - Total GCS

- **Serum HCO_3 (venous mmol/L) - not preferred, use if no ABG's**

B) AGE POINTS

Appropriately assign Age Points as follows. Remember to carefully calculate the patient's age.

Age (years)	**Points**
< 44	0
45-54	2
55-64	3
65-74	5
> 75	6

C) CHRONIC HEALTH POINTS

- Appropriately assign Chronic Health Points using the definitions listed below. If a patient has evidence of one or more of the following criteria **(1-5),** points will be scored as follows:

  a) Non-operative or emergency postoperative patients = **5 points**

  b) Elective postoperative patients = **2 points**

  c) If the patient has no chronic health states **= 0 points**

- "*Emergency postoperative patient*" will be defined as a patient who has received surgery required immediately to correct a life-threatening condition.

- A total of either "0", "2", or "5" points can be scored for this section. Points are not calculated based on the number of chronic health conditions.
- The patient's complete medical history / hospital chart should be reviewed for assessment of this category.
- Organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and confirm to the following definitions:

1) LIVER

Biopsy proven cirrhosis and documented portal hypertension, episodes of past upper GI bleeding attributed to portal hypertension or prior episodes of hepatic failure/encephalopathy/coma.

2) CARDIOVASCULAR

New York Heart Class IV. Dyspnea at rest (patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest).

3) RESPIRATORY

Chronic restrictive obstructive vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg) or respiratory dependency.

4) RENAL

Receiving chronic dialysis.

5) IMMUNOCOMPROMISED

The patient has received therapy that suppresses resistance to infection, (e.g. immunosuppression, chemotherapy, radiation, long term or recent high dose steroids) or has a disease that is sufficiently advanced to suppress resistance to infection, (e.g. leukemia, lymphoma, multiple myeloma, AIDS).

The definition for long-term high dose steroids is:

a) Greater than 0.3 mcg/kg/day of Prednisone or its equivalent daily for 6 months.

b) Use of active radio- or chemotherapy in the previous year.

REFERENCES AND RESOURCES

1. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13(10):818-829

2. Livingston BM, Mackenzie SJ, MacKirdy FN, Howie JC. Should the presedation Glasgow Coma Scale value be used when calculating Acute Physiology and Chronic Health Evaluation scores for sedated patients? Crit Care Med 2000; 28(2):389-394

3. Medical Information Eli Lilly Canada Inc. Use of APACHE II in the PROWESS Trial.

4. Computer assisted APACHE tool: http://www.sfar.org/scores2/apache22.html.

APACHE II Calculation Worksheet (from PROTECT Study)

A. Physiologic Variables Points

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE				PT SCORE
	4	3	2	1	0	1	2	3	4	
Temperature - rectal (°C)	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9	
MAP (mmHg)	≥ 160	130-159	110-129		70-109		50-69		≤ 49	
Heart Rate	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39	
Respiratory Rate (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5	
Oxygenation: [A-aDO_2 = (FiO_2 x 710) – (PCO_2 x 1.25) – PO_2]					FiO_2 =		PCO_2 =		PO_2 =	
a. FiO_2 ≥ 0.5 record A-aDO_2	≥ 500	350-499	200-349		< 200					
b. FiO_2 < 0.5 record only PaO_2					PO_2 > 70	PO_2 61-70		PO_2 55-60	PO_2 < 55	
Arterial pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15	
Serum Na (mmol/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110	
Serum K (mmol/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5	
Serum Creatinine (umol/L)	> 305	170-304	130-169		53-129		<53			
Hematocrit (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20	
WBC (total/mm^3)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1	
Glasgow Coma Score (GCS)	Score = 15 minus actual GCS (see below)									
Serum HCO_3 (venous mmol/L) - not preferred, use if no ABG's	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.0	< 15	
Creatinine double points for ACUTE Renal Failure	ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points =									

B. Age Points - Assign points to age as follows:

AGE (yrs)	POINTS
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6
AGE SCORE =	

C. Chronic Health Points - If the patient has a history of severe organ system insufficiency (see below) or is immunocompromised assign points as follows:

a. For nonoperative or emergency postoperative pt – 5 points
b. For elective postoperative pt – 2 points

CHRONIC HEALTH SCORE =

D. APACHE II SCORE - Sum of A + B + C

A. APS points	
B. Age points	
C. Chronic Health points	
APACHE II SCORE =	

GLASGOW COMA SCALE		
Parameter	Response	Points Assigned (please circle)
Eyes Open	Spontaneously	4
	On spoken command	3
	On pain	2
	No response	1
Best Motor Response	To spoken command	6
	To painful stimulus:	
	Localized pain	5
	Flexion withdrawal	4
	Flexion abnormal	3
	Extension	2
	No response	1
Best Verbal Response	*(Not on ventilator)*	
	Oriented & converses	5
	Disoriented & converses	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
	(On ventilator)	
	Appears oriented	5
	Questionably oriented	3
	Generally unresponsive	1
	TOTAL GCS =	

DEMOGRAPHICS AND COMORBIDITIES FORM 2.1 (Continued)

- Admission Category to ICU:
    - for the purposes of this question, a "surgical" admission involves any patient except surgical trauma that came out of the operating room to the ICU, or had surgery within 24h of ICU admission (*for patients admitted due to trauma, check the "trauma" box even if they come through operating room).*
    - therefore, even if a patient is admitted to a surgical service, if they have not had any surgery then they should be classified under another category as appropriate.
- Reason that Patient was Admitted to ICU:
    - please check all that apply. For example, if patient is admitted with COPD exacerbation plus pneumonia, and pneumonia was associated with a positive blood culture then you would check all 3: COPD, pneumonia, and bloodstream infection.

- Comorbidities
    - check yes for all of the underlying illnesses that are noted in the patient's past medical history, or become apparent during the current hospital admission.
    - this comorbidity list also includes elements of the APACHE II score.
    - to meet NYHA=IV criteria for congestive heart failure the patient must be severely limited and experience symptoms even at rest.
    - to meet criteria for "liver disease – cirrhosis/portal HTN" the patient must have biopsy proven cirrhosis with portal hypertension, or episodes of past GI bleeding attributed to portal hypertension (esophageal varices), or prior episodes of hepatic failure, encephalitis, or coma from liver failure.
    - to meet criteria for severe lung disease:
        - the patient must have chronic lung disease of any type
            - restrictive (e.g. pulmonary fibrosis)
            - obstructive (e.g. COPD) or
            - vascular (e.g. pulmonary hypertension)
        - and they must also have severe exercise restriction (unable to climb stairs or perform household duties) OR respiratory dependency OR documented chronic hypoxemia OR documented chronic hypercapnea (high PCO_2).

DEMOGRAPHICS AND COMORBIDITIES FORM 2.2 (page 2 of 2)

- Date & time first blood culture 'collected (index blood culture) for which patient is enrolled in study:
    - the 'first positive blood culture' refers to the positive blood culture for which the patient was enrolled in the study.
    - the patient may have had prior negative cultures which wouldn't count as first culture.
    - the patient may even have had prior positive cultures during that admission that didn't count as first positive culture because they didn't meet inclusion/exclusion criteria for the study (for example yielded a non-pathogenic organism or a contaminant).

- the "date and time first positive blood culture collected" are usually reported with the microbiology lab result.
    - the "date and time that the blood culture result was finalized" means when the susceptibility is reported for the index organism.
    - date and time finalized is usually reported with the microbiology lab result; this may be listed as "date finalized" or "date last updated" or "date reported" or with some other similar terminology in your institution.
- where was the sample drawn from? This may be labeled in the microbiology result, or documented in nursing notes.
- the "number of positive blood culture sets from the index blood culture day" should be reported.
    - 'positive blood culture sets' means total number of positive blood culture tests **within 24 hours** of first positive blood culture (index blood culture) collected for which patient is enrolled in the study. This will include index blood culture also.
    - for example, the patient may have had three blood culture sets sent within 24 hrs, and 2 out of the 3 may have grown *E .coli* (then you would fill in the number as 2).
    - note: each blood culture set usually includes two bottles (an aerobic bottle and an anaerobic bottle). If one or both of these are positive, this would count as a positive blood culture set except possible contaminants.
- names of organisms
    - include all organisms isolated in the first blood culture set, *as well as* other positive blood culture sets within 24 hours of the first positive blood culture.
    - codes for the organisms are listed in the table below.
    - if organism is not captured in this list please contact the central study coordinator (asgar.rishu@sunnybrook.ca) at Sunnybrook Health Sciences Centre to add that organism to the

list (you will then need to remember to re-enter that new organism code when it is available the next day).

ORGANISM CODES

Name	Code	Name	Code
Abiotrophia/Granulicatella species	001	*Capnocytophaga species*	028
Acinetobacter baumannii	002	*Cardiobacterium species*	029
Acinetobacter lwoffii	003	*Chromobacterium species*	030
Acinetobacter xylosoxidans	004	*Chryseobacterium species*	031
Acinetobacter species	005	*Citrobacter freundii*	032
Acremonium species	006	*Citrobacter koseri*	033
Actinobacillus species	007	*Citrobacter species*	034
Actinomyces species	008	*Clostridium difficile*	035
Aerococcus species	009	*Clostridium perfringens*	036
Aeromonas species	010	*Clostridium septicum*	037
Alpha haemolytic streptococci	011	*Clostridium species*	038
Aspergillus species	012	*Corynebacterium species*	039
Bacillus species	013	*Cryptococcus species*	040
Bacteroides fragilis	014	*Cyclospora species*	041
Bacteroides species	015	*Diphtheroid bacilli*	042
Bifidobacterium species	016	*Edwardsiella species*	043
Blastomyces species	017	*Ehrlichia species*	044
Bordetella species	018	*Enterobacter aerogenes*	045
Borrelia species	019	*Enterobacter cloacae*	046
Brucella species	020	*Enterobacter species*	047
Burkholderia cepacia	021	*Enterococcus faecalis*	048
Campylobacter species	022	*Enterococcus faecium*	049
Candida albicans	023	*Enterococcus species*	050
Candida glabrata	024	*Erysipelothrix species*	051
Candida parapsilosis	025	*Escherichia coli*	052
Candida tropicalis	026	*Escherichia species*	053
Candida species	027	*Eubacterium species*	054

Flavobacterium species	055	*Nocardia species*	085
Fusobacterium species	056	*Pantoea species*	086
Gemella species	057	*Pediococcus species*	087
Granulicatella species	058	*Peptococcus species*	088
Hemophilus influenzae	059	*Peptostreptococcus species*	089
Haemophilus species	060	*Plesiomonas species*	090
Hafnia species	061	*Pneumocystis carinii*	091
Helicobacter species	062	*Porphyromonas species*	092
Isospora species	063	*Prevotella species*	093
Kingella species	064	*Propionibacterium species*	094
Klebsiella oxytoca	065	*Proteus mirabilis*	095
Klebsiella pneumoniae	066	*Proteus species*	096
Klebsiella species	067	*Proteus vulgaris*	097
Kluyvera species	068	*Providencia species*	098
Lactobacillus species	069	*Pseudomonas aeruginosa*	099
Leuconostoc species	070	*Pseudomonas species*	100
Listeria monocytogenes	071	*Raoultella species*	101
Micrococcus species	072	*Salmonella enteritidis*	102
Microsporum species	073	*Salmonella species*	103
Moraxella catarrhalis	074	*Salmonella typhi*	104
Moraxella species	075	*Salmonella typhimurium*	105
Morganella morganii	076	*Serratia marcescens*	106
Morganella species	077	*Serratia species*	107
Mycobacterium tuberculosis	078	*Shigella species*	108
Mycobacterium species	079	*Sphingobacterium species*	109
Mycobacterium szulgai	080	*Staphylococcus* (Coagulase negative)	110
Mycoplasma species	081	*Staphylococcus aureus* (including MRSA)	111
Neisseria gonorrhoeae	082	*Staphylococcus epidermidis*	112
Neisseria meningitidis	083	*Staphylococcus haemolyticus*	113
Neisseria species	084	*Staphylococcus lugdenensis*	114

Staphylococcus schleiferi	115	*Streptomyces species*	130
Staphylococcus species	116	*Torulopsis species*	131
Stenotrophomonas maltophilia	117	*Trichoderma species*	132
Stomatococcus species	118	*Trichophyton species*	133
Streptococcus anginosus group	119	*Trichosporon species*	134
Streptococcus bovis/Gallolytics	120	*Ureaplasma species*	135
Streptococcus pneumoniae	121	*Veillonella species*	136
Streptococcus salivarius	122	*Vibrio species*	137
Streptococcus, group A	123	*Weeksella species*	138
Streptococcus, group B	124	*Wolinella species*	139
Streptococcus, group C	125	*Yersinia species*	140
Streptococcus, group D	126	*Yeast*	141
Streptococcus, group G	127	Other	142
Streptococcus viridians (Viridans group streptococcus)	128	**Not in the list→** email Sunnybrook Research Coordinator asgar.rishu@sunnybrook.ca	
Streptococcus species	129		

Organisms are color coded alphabetically.

INDEX CULTURE AND POTENTIAL SOURCE OF INFECTION– FORM 2.3

- potential source of bacteremia:
- this form should be filled by the treating team unless source is clearly documented on the medical chart
    - ask the treating team (fellow and above staff) to check the most appropriate response for each item.
    - if the team is sure about a particular source of infection, check others as unlikely or not a possible source.
    - each source should have a response.
    - if the team considered a list of possible sites or there is evidence of multiple sites of infection then check all that are referred to.
    - if the potential source is clearly documented in the chart for which patient is being treated, fill out this form on your own.
    - if the team is not sure about source or documented that the source was undefined, please check "undefined (primary bacteremia)"
    - in case of any doubt, contact your site investigator.

Pre-Hospitalization Admission Clinical Frailty Scale Form – FORM 2.4

- please choose the most appropriate response.
- assign score as per pre-hospital status.
- considering the patient's pre-hospital admission status, please select the highest score from the descriptions from 1 to 9.
- scoring frailty in people with **dementia**: The degree of frailty corresponds to the degree of dementia.
    - common symptoms in **mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.
    - in **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
    - in **severe dementia**, they cannot do personal care without help.

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OUTCOME – FORM 3.1

- Mechanical ventilation:
    - mechanical ventilation free days will be defined as being off of mechanical ventilator for 48 hours. If a patient is re-intubated within 48 hours of extubation, consider mechanically ventilated for the period between.

- Outcome: Survival and Length of Stay
    - date of ICU discharge refers to discharge from ICU to a non-ICU ward.
    - a patient will *not* yet be considered discharged from ICU if they are
        - transferred from level III (highest acuity) to level II ("step-down/step-up") ICU unless they are not under ICU (ICU physician/team) care any longer
        - transferred from level II to level III ICU
        - transferred from level II or level III ICU to some other location but still under primary care of ICU physician/team
    - re-admission to ICU will be defined as admission to ICU within 48 hours of discharge from the ICU within the same hospitalization after inclusion in this study.

- 90 day outcome
    - 90 day assessment date will be calculated from the positive blood culture date (index blood culture) for which patient is enrolled in this study (culture collection date + 90).
    - 90 day assessment date is NOT calculated from ICU/hospital admission/discharge date.
    - 90 day assessment date entered on the CRF should be the actual 90 day assessment date and not the date when you call/are able to contact patient/family.
        - death on or before day 90 should be recorded as "dead"
    - most patients will be out of hospital at day 90, so remember to note down the contact details for follow-up in a secure place
    - 90 days assessment will be done only for **Eligible Randomized** patients enrolled in this study and not for Eligible Non-Randomized patients.
    - Remember to obtain the primary contact number and an alternative contact number for 90 day outcome follow-up call.

ANTIMICROBIAL SUSCEPTIBILITIES OF ORGANISMS IN INDEX BLOOD CULTURE (FORMS 4.1 – 4.5)

- the antibiotic susceptibilities available for each organism will differ according to the organism (and may also differ according to the hospital's microbiology lab procedures).
- for each available antibiotic susceptibility result please enter susceptible (S), intermediate (I) or resistant (R).
- if there are 2 different organisms in the index blood culture, then please fill out a separate form (Form 4.2, 4.3…) for each organism. If the same organism appears in multiple sets within 24 hours, fill only one form.
- the microbiology lab at your hospital will usually only report the results of some of the antibiotics they have tested (they often suppress the results for some of the more expensive and broad spectrum drugs).
    - the most efficient and accurate approach will probably be to ask the lab for a printout of the full antibiotic susceptibility test results for the bacteria identified in the index blood cultures for each patient (including all antibiotics tested).
    - full susceptibility report is important for treatment duration adjudication and also for the antimicrobial resistance pattern which is the study secondary outcome.
- there are some bacteria for which antibiotic susceptibility testing is not routinely performed, in which case you can just enter the organism's ID number in the top boxes without checking any of the antibiotic susceptibility boxes.
    - examples of this include
        - Beta-hemolytic streptococcus, Group A and
        - Beta-hemolytic streptococcus, Group B

    because they are both universally susceptible to penicillin (so there is no role for testing)

ANTIMICROBIAL TREATMENT FORMS 5.1-5.4

- obtain from medication administration record (not doctors orders).
- please enter dates in sequence (ascending order form the start date).
- include any antimicrobial treatment that overlaps any part of the period from 3 days prior to the first (index blood culture) blood culture up to actual stop date.
- include any antimicrobial treatment that overlaps this time interval, even if you think it is being given for treatment of some other unrelated infection.
- include an entry even if antimicrobial is given as a single one time dose.
- record all dose, route, frequency changes as a new entry.
- dose should be recorded in milligrams (for example, for 4.5g write 4500mg).
- for penicillin dose conversion, 1 MU= 625mg.
- if antimicrobial was started prior to admission date and the start date is unknown (for example, a chronic prophylactic antimicrobial) then enter as missing value.
- if an antimicrobial is still ongoing at the time of hospital discharge, check the 'yes' box for 'continued after discharge'. You should enter the post-discharge stop date as prescribed on the discharge prescription. Enter missing only if the stop date is not available/confirmed from the discharge prescriptions/physician notes at the time of hospital discharge/or hospital discharge summary.
    - hospital discharge date should not be entered as antibiotic stop date for patients discharged before completing the study assigned treatment duration.
- antimicrobial codes are listed in the table below.
- if antimicrobial is not captured in this list please email the central study coordinator at Sunnybrook and they will organize to add that antimicrobial to the list. You will then need to remember to re-enter that new code when it's available the next day.

Antimicrobial Codes

Antimicrobial name	Antimicrobial Code	Antimicrobial name	Antimicrobial Code
Amikacin	01	Levofloxacin	34
Amoxicillin	02	Linezolid	35
Amoxicillin-clavulanate	03	Meropenem	36
Ampicillin	04	Metronidazole	37
Ampicillin-sulbactam	05	Moxifloxacin	38
Azithromycin	06	Nitrofurantoin	39
Aztreonam	07	Norfloxacin	40
Cefaclor	08	Nafcillin	41
Cefadroxil	09	Oxacillin	42
Cefazolin	10	Penicillin G	43
Cefepime	11	Penicillin V	44
Cefixime	12	Pentamidine	45
Cefotaxime	13	Piperacillin	46
Cefprozil	14	Piperacillin-tazobactam	47
Cefoxitin	15	Polymyxin B	48
Ceftazidime	16	Tetracycline	49
Ceftriaxone	17	Ticarcillin-clavulanate	50
Cefuroxime	18	Tigecycline	51
Cephalexin	19	Tobramycin	52
Carithromycin	20	Trimethoprim	53
ClIndamycin	21	Trimethoprim-sulfamethoxazole	54
Cloxacillin	22	Vancomycin	55
Ciprofloxacin	23	Amphotericin	56
Colistin/colistimethate	24	Anidulafungin	57
Dapsone	25	Caspofungin	58
Daptomycin	26	Fluconazole	59
Dicloxacillin	27	Itaconazole	60
Doripenem	28	Micafungin	61
Doxycycline	29	Voriconazole	62
Ertapenem	30	**Not in the list→** email Sunnybrook Research Coordinator asgar.rishu@sunnybrook.ca	
Erythromycin	31		
Gentamicin	32		
Imipenem	33		

Antimicrobials are color coded alphabetically and Antifungals are listed at the end

Antimicrobial Route and Frequency Codes:

Drop Down List for ROUTE	**Drop Down List for FREQUENCY**
IV -intravenous PO -per os NG -nasogastric tube GT -gastric tube or jejunostomy tube IM -intramuscular IP -intraperitoneal IT -intrathecal Oth -other note: do not include topical antimicrobials, eye drops/ointments, otic/ear drops, etc.	one time dose q1h q2h q3h q4h q5h q6h q8h q12h q18h q24h q36h q48h q72h q96h Oth -other Note: if Antimicrobial being given less frequently than q96h, then enter each dose as new one time dose *QID enter as Q6h *TID enter as Q8h *BID enter as Q12h *OD enter as Q24h *QHS enter as Q24h

SOURCE CONTROL PROCEDURES FORM 6.1

- some bloodstream infections must be treated not only with antimicrobials but also with interventions/procedures to control the underlying source of infection.
- please check all source control procedures performed for the patient's first bloodstream infection (i.e. for the bloodstream infection that led to study enrolment).
- for procedures/interventions done more than once (example: Foley (urinary) catheters or central line catheters), document the date procedure is first performed.
- most source control procedures will be documented in doctor's progress notes, but some may be evident under nursing notes (e.g., line removal) or radiologic or operative procedure notes.
- one source control procedure that will be most common but also most difficult to find in the notes will be removal of vascular catheters.
    - even if removal of the vascular catheters are not documented in the chart, you can also use these items as alternative evidence of catheter removal:
        - evidence of insertion of a new catheter of the same type.
        - evidence that a catheter tip has been sent for culture to the microbiology lab.
- ERCP is endoscopic retrograde cholangiopancreatography.

BLOOD CULTURE RESULTS FROM INDEX CULTURE TO 30 DAYS LATER- FORMS 7.1-7.12

- you need to fill in all of the blood culture results from first positive blood culture (including culture set for which patient was included) up to 30 days.
- this information will help identify how quickly the bloodstream infection was cleared, whether or not a relapse of the bacteremia occurred (same organism in blood again), and whether any other bloodstream infections occurred with other organisms during the study.
- dates and times refer to blood culture collection (not blood culture final reports).
- the organism codes are available in the table above.
- please complete the corresponding susceptibility form (Form 7.3-7.12) for all the organisms that are reported on Form 7.1 - 7.2 (similar to form 4.1-4.5)

ANY OTHER POSITIVE CULTURE RESULTS FORM 8.1-8.2 AND FORM 9.1-9.8

- record any other **POSITIVE** microbiology results other than the blood microbiology for up to **30** days from the index blood culture date.
- document all the sensitivity results for the corresponding organism on Forms 9.1-9.8.
- if there are two different organism from the same specimen, use separate sheets to record susceptibility.

WITHDRAWAL FORM 10.1 (page 1 of 1)

- complete this form if a patient is withdrawn from the study due to one of the following reasons:
    - patient had relevant exclusion criteria present prior to randomization
        - Please specify exclusion criteria:_____.
    - consent withdrawn
        - patient
        - physician .
        - legal SDM other family member.
        - other (specify):_____.
    - duplicate randomization, specify first actual patient ID.
    - one day of study drug administered only.
- in case of withdrawal, if permitted by the patient or substitute-decision maker, continue full data collection as would be done for non-withdrawn patients on the basis of **intention to treat** principle.

ANTIMICROBIAL-RELATED ADVERSE EVENTS – FORM 11.1

- to be completed for up to 30 days post initiation of adequate antibiotic treatment
- to be considered anaphylaxis, the patient must have had >=1 of the following 3 criteria that a medical team member attributed to an antimicrobial
    - 1. acute onset of skin or mucosal tissue changes (hives, itching/flush, lip/tongue/uvula swelling) over minutes/hours, accompanied by
        - respiratory compromise (dyspnea, wheeze, stridor, hypoxemia), AND/OR
        - reduced blood pressure or symptoms/signs of end organ dysfunction from shock
    - 2. rapid onset of two or more of the following
        - involvement of the skin-mucosa (hives, itch//flush, swollen lips/tongue/uvula)
        - respiratory compromise
        - reduced BP or associated symptoms/signs
        - persistent gastrointestinal symptoms/signs (crampy abdominal pain, vomiting)
    - 3. reduced blood pressure after exposure to a known allergen for that patient
- to be considered antimicrobial-associated kidney injury, a medical team member must have attributed the renal injury to the antimicrobial, and the severity of the kidney injury must meet one of these (RIFLE criteria):
    - doubling of creatinine, OR
    - GFR decrease >50% from stable baseline before antimicrobial administered, OR
    - urine output <0.5mL/kg/h x 12h
- to be considered antimicrobial-associated liver injury, a medical team member must have attributed the liver injury to the antimicrobial, and the severity must meet this FDA criteria for hepatic adverse events:
    - ALT> 3x the upper limit of normal in your laboratory
- enter a date if one of these events was noted by a physician and attributed to the antimicrobial medications during the antibiotic treatment for initial bacteremia, after the completion of antibiotic treatment duration for bacteremia but treating team continued antibiotics beyond the study duration or after the completion of assigned treatment duration but due to another antibiotic unrelated to bacteremia.

TIME COURSE - FORMS 12.0 – 12.14

- daily data is to be collected for up to 14 days or discharge from hospital whichever is earlier
- daily data for up to 14 days is to be collected even if a patient is randomized to 7 day arm
- day 0 date is considered the date of collection of first positive blood culture (index positive culture) for which patient was enrolled in study and should be same as the index culture collection date on form 2.2
- all variables should be collected from day 0 up to day 14 even if patient is transferred from ICU
- all measurements should be of the most extreme abnormal value from that day (between 08:00 that day and 07:59 the following day, *, or a 24 day that most reflects your own ICU practice, and is consistent over time*)
    - this would include *highest* values for:
        - FiO_2, resp rate, creatinine, bilirubin, heart rate, core temperature, white blood cell count
    - this would mean *lowest* values for:
        - PaO_2, platelet count, Glasgow coma score, MAP, SBP, DBP (**please use the corresponding SBP and DBP values for the lowest MAP**)
    - MAP, SBP and DBP should be recorded from the same reading and not worst values from separate readings.
- following discharge from ICU, MAP does not need to be entered (please enter SBP and DBP and then MAP will be calculated from these).

- Glasgow Coma Scale (GCS):

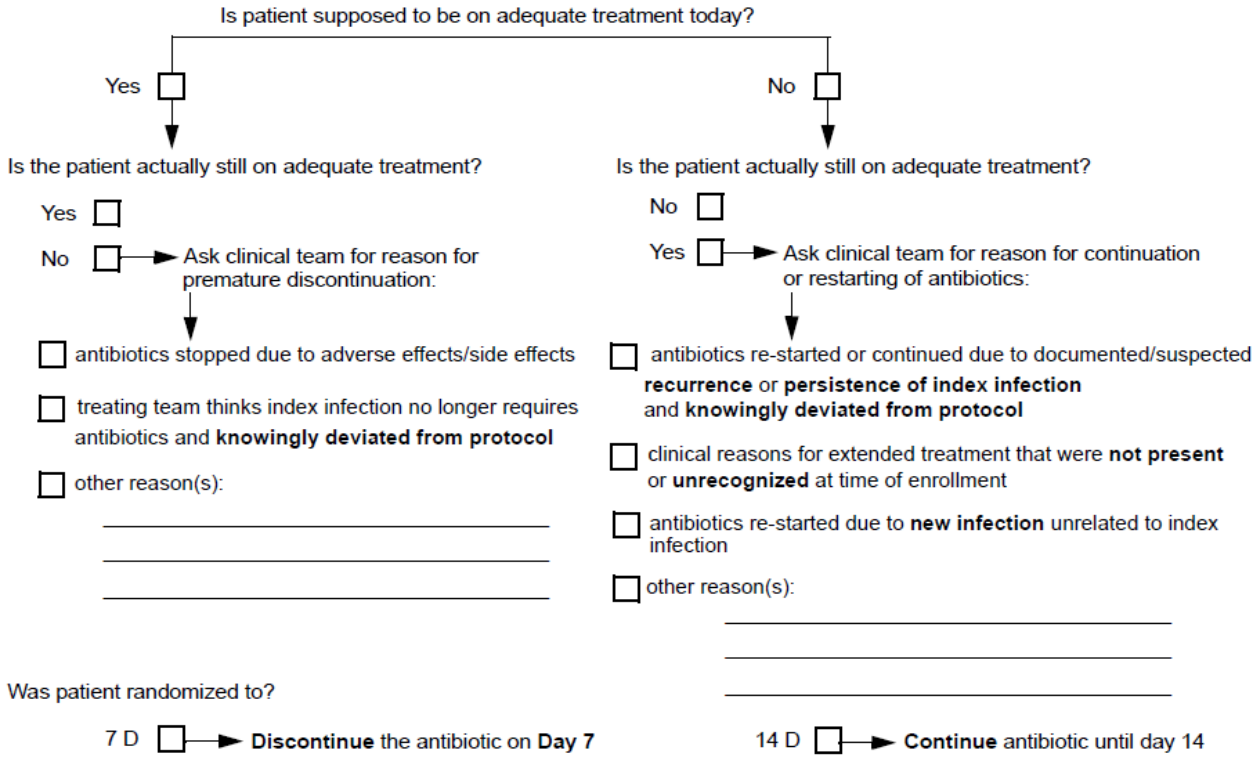
    - see under APACHE above

- mechanical ventilation free days will be defined as being off of mechanical ventilator for 48 hours. If a patient is intubated within 48 hours of extubation, consider mechanically ventilated for the period between.

- vasopressor free days will be defined as being off of vasopressors for 48 hours. If a patient is re-started on vasopressors within 48 hours, consider being on vasopressors for the period between.

STUDY DRUG RELATED DAILY DATA FORM 13.1 – 13.16

- Research Coordinator to Assess Patient Daily (each AM) for **16 days after Randomization or until hospital discharge**.
    - if a patient is discharged form hospital before completing study assigned duration and you know that there is a deviation, please complete form 16 to capture the deviation.
- Form 13.1 – 13.16 (Protocol Violation/Deviation) should be entered into e-database (iDataFax) on daily basis after randomization. This form will be validated based on data entered on form 5.1 (Antimicrobial treatment form).
- you will need to print 16 pages of this form to be used for daily "STUDY DRUG RELATED DAILY DATA" collection.
- current date for the first form (13.1) is when the patient is randomized and will be the same as date of randomization on Form 1.2.
    - sites using actual date and time of randomization due to time difference should use the same dates on both forms 1.2 and 13.1.
- research coordinator with site investigator to ensure clinical team adheres to study treatment duration protocol.
- if clinical team proposes non-study treatment duration protocol antibiotic choice, research coordinator and/or site investigator to follow-up with clinical team that am to continue appropriate antibiotics for study treatment arm.
- if clinical team deviates from study treatment duration protocol, research coordinator to follow below algorithm:



CDC Criteria for Infectious Syndromes

[From Horan *AJIC* 2008]

Urinary Tract Infection

Must meet at least 1 of the following criteria:

1. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever >38deg Celsius, urgency, frequency, dysuria, or suprapubic tenderness
   AND
   Patient has a positive urine culture with >=10^5 microorganisms/mL of urine with no more than 2 species of microorganisms
2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever >38 degrees Celsius, urgency, frequency, dysuria, or suprapubic tenderness
   AND
   at least 1 of the following
   a. positive dipstick for leukocyte esterase and/or nitrate
   b. pyuria (urine with >=10 WBC/mm^3 or >=3 WBC/high-powered field of unspun urine
   c. organisms on gram stain of unspun urine
   d. at least 2 urine cultures with repeated isolation of the same uropathogen (gram negative bacteria or *Staphylococcus saprophyticus*) with >=10^2 colonies/mL in non-voided specimens
   e. <=10^5 colonies/mL of a single uropathogen (gram negative bacilli or *S. saprophyticus*) in a patient being treated with an effective antimicrobial agent for urinary tract infection
   f. physician diagnosis of a urinary tract infection
   g. physician institutes appropriate therapy for a urinary tract infection

Intra-Abdominal Infection
(including gallbladder, bile ducts, liver, spleen, pancreas, peritoneum, subphrenic, sub-diaphragmatic, or other intra-abdominal space)

Must meet at least 1 of the following criteria:

1. Patient has organisms cultured from purulent material from intra-abdominal space obtained during a surgical operation or needle aspiration.
2. Patient has abscess or other evidence of intra-abdominal infection seen during a surgical operation or histopathologic examination
3. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever >38 degrees Celsius, vomiting, abdominal pain, or jaundice
   AND
   at least 1 of the following:
   a. organisms cultured from drainage from surgically placed drain (e.g, closed suction drainage system, open drain, T-tube drain)
   b. organisms seen on gram stain of drainage or tissue obtained during surgical procedure or needle aspiration
   c. organisms cultured from blood *and* radiologic evidence of infection (e.g, abnormal findings on ultrasound, CT scan, MRI or radiolabel scans or abdominal xray)

[note: non-infectious pancreatitis should not be included; viral hepatitis should not be included]

Skin and Soft Tissue Infection
Must meet at least 1 of the following criteria:

1. Patient has purulent drainage, pustules, vesicles or boils.
2. Patient has at least 2 of the following signs/symptoms with no other recognized cause: pain or tenderness, localized swelling, redness, or heat
   AND
   at least 1 of the following:
   a. organisms cultured from aspirate or drainage from affected site: if organisms are normal skin flora (i.e. diptheroids/*Corynebacteria* spp, *Bacillus* spp., *Proprionibacterium spp*., coagulase negative staphylococci (including *Staph epidermidis*), viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp.) they must be a pure culture
   b. organisms cultured from blood
   c. positive antigen test performed on infected tissue or blood (e.g., herpes simplex, varicella zoster, *H. influenzae, N. meningitidis*)
   d. multinucleated giant cells seen on microscopic examination of tissue
   e. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen.

[note: c,d,e are not relevant for the purposes of this study]

Pneumonia
Must meet both radiologic and clinic criteria.

Radiologic:
Two or more serial chest radiographs with at least 1 of the following

1. new or progressive and persistent infiltrate (or 'opacification' or 'air space disease')
2. consolidation
3. cavitation

Clinical:
At least 1 of the following:

1. fever (>38 degrees Celsius) with no other recognized cause
2. leukopenia (<4 WBC/$mm^{3+)}$ or leukocytosis (>12WBC/mm^3)
3. altered mental status for adults >70 years old

AND
At least 2 of the following

1. new onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements
2. new onset of worsening cough, or dyspnea or tachypnea
3. rales or bronchial breath sounds
4. worsening gas exchange (PaO_2/FiO_2 ratio <=240), increased oxygen requirements, or increased ventilator demand)

Central Vascular Catheter Related Bloodstream Infection

Must have a central vascular catheter+* and meet 1 of the following:

1. Patient has a recognized pathogen cultured from one or more blood cultures
   AND
   Organism cultured form blood is not related to infection at another site.
2. Patient has a common commensal (i.e., diptheroids [*Corynebacterium spp.* not *C. diptheriae*], *Bacillus spp.* [not *B. anthracis*], *Propionobacterium spp.*, coagulase negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., and *Micrococcus spp.*) cultured from **2 or more** blood culture sets drawn on separate occasions
   AND
   Patient has at least 1 of the following signs or symptoms: fever>38 degrees Celsius, chills or hypotension
   AND
   Signs/symptoms are not related to infection at another site

[note: for purposes of our study, some episodes of bloodstream infection will be labeled as 'unknown/undetermined'. We will not lump all unexplained bacteremias into category of central vascular catheter related bloodstream infection]

*note: a central vascular catheter is an intravascular catheter that terminates at or close to the heart or in one of the great vessels which is used for infusion, withdrawal of blood, or hemodynamic monitoring. The great vessels include the aorta, pulmonary artery, superior vena cava, inferior vena cava, brachiocephalic veins, internal jugular veins, subclavian veins, external iliac veins, common iliac veins, and femoral veins.