

**Additional file 6: Definitions of included serious adverse effects**

Each serious adverse effect included was defined as a set of MedDRA preferred terms, as reported in Table A6. For most of the adverse effects the starting point was one or several Standardised MedDRA Queries (SMQs), from which terms were chosen by the clinical expert (IRE) on the basis that they corresponded to the intended adverse effect. To reduce workload, the selection was made from the set of terms listed on any of the methylprednisolone reports assigned to either the low- or the high-dose group. This means that if a term belonging to the considered SMQ is not included here, it might not have been actively excluded; rather, it might not even have been considered.

**Table A6. Definitions of included serious adverse effects, as sets of MedDRA preferred terms.**

| Adverse effect       | SMQ used as basis <sup>a</sup> | Algorithm      | MedDRA preferred term <sup>a</sup> | Term category <sup>b</sup> | Term implies life-threatening reaction <sup>c</sup> | Term implies persistent disability <sup>c</sup> |
|----------------------|--------------------------------|----------------|------------------------------------|----------------------------|-----------------------------------------------------|-------------------------------------------------|
| Acute severe allergy | Anaphylactic reaction (broad)  | A or (B and C) | Anaphylactic reaction              | A                          | Yes                                                 | No                                              |
|                      |                                |                | Anaphylactic shock                 | A                          | Yes                                                 | No                                              |
|                      |                                |                | Anaphylactoid reaction             | A                          | Yes                                                 | No                                              |
|                      |                                |                | Bronchospasm                       | B                          | No                                                  | No                                              |
|                      |                                |                | Laryngeal oedema                   | B                          | No                                                  | No                                              |
|                      |                                |                | Laryngospasm                       | B                          | No                                                  | No                                              |
|                      |                                |                | Angioedema                         | C                          | No                                                  | No                                              |
|                      |                                |                | Face oedema                        | C                          | No                                                  | No                                              |
|                      |                                |                | Periorbital oedema                 | C                          | No                                                  | No                                              |
|                      |                                |                | Swelling face                      | C                          | No                                                  | No                                              |
|                      |                                |                | Urticaria                          | C                          | No                                                  | No                                              |

|                              |                                                            |    |                                      |    |     |                 |
|------------------------------|------------------------------------------------------------|----|--------------------------------------|----|-----|-----------------|
| Diabetes                     | Hyperglycaemia / new onset diabetes (narrow)               | NA | Blood glucose increased              | NA | No  | No              |
|                              |                                                            |    | Diabetes mellitus                    | NA | No  | Yes             |
|                              |                                                            |    | Diabetes mellitus inadequate control | NA | No  | No <sup>d</sup> |
|                              |                                                            |    | Diabetic hyperglycaemic coma         | NA | Yes | No <sup>d</sup> |
|                              |                                                            |    | Diabetic ketoacidosis                | NA | Yes | No <sup>d</sup> |
|                              |                                                            |    | Glucose tolerance impaired           | NA | No  | No              |
|                              |                                                            |    | Glycosuria                           | NA | No  | No              |
|                              |                                                            |    | Hyperglycaemia                       | NA | No  | No              |
|                              |                                                            |    | Type 1 diabetes mellitus             | NA | No  | Yes             |
|                              |                                                            |    | Type 2 diabetes mellitus             | NA | No  | Yes             |
| Cardio-pulmonary distress    | Haemodynamic oedema, effusions and fluid overload (narrow) | NA | Acute pulmonary oedema               | NA | Yes | No              |
|                              |                                                            |    | Pleural effusion                     | NA | No  | No              |
|                              |                                                            |    | Pulmonary oedema                     | NA | Yes | No              |
|                              | Acute central respiratory depression (broad)               | NA | Acute respiratory distress syndrome  | NA | Yes | No              |
|                              |                                                            |    | Acute respiratory failure            | NA | Yes | No              |
|                              |                                                            |    | Apnoea                               | NA | Yes | No              |
|                              |                                                            |    | Cardiopulmonary failure              | NA | Yes | No              |
|                              |                                                            |    | Cyanosis                             | NA | No  | No              |
|                              |                                                            |    | Dyspnoea                             | NA | No  | No              |
|                              |                                                            |    | Respiratory arrest                   | NA | Yes | No              |
|                              |                                                            |    | Respiratory depression               | NA | No  | No              |
|                              |                                                            |    | Respiratory distress                 | NA | No  | No              |
|                              |                                                            |    | Respiratory failure                  | NA | Yes | No              |
| Gastrointestinal haemorrhage | Gastrointestinal haemorrhage (narrow)                      | NA | Duodenal ulcer haemorrhage           | NA | No  | No              |
|                              |                                                            |    | Enterocolitis haemorrhagic           | NA | No  | No              |
|                              |                                                            |    | Gastric haemorrhage                  | NA | No  | No              |
|                              |                                                            |    | Gastric ulcer haemorrhage            | NA | No  | No              |
|                              |                                                            |    | Gastritis haemorrhagic               | NA | No  | No              |
|                              |                                                            |    | Gastrointestinal haemorrhage         | NA | No  | No              |
|                              |                                                            |    | Gastrointestinal ulcer haemorrhage   | NA | No  | No              |
|                              |                                                            |    | Haematemesis                         | NA | Yes | No              |
|                              |                                                            |    | Haematochezia                        | NA | No  | No              |
|                              |                                                            |    | Intestinal haemorrhage               | NA | No  | No              |
|                              |                                                            |    | Intra-abdominal haematoma            | NA | No  | No              |
|                              |                                                            |    | Melaena                              | NA | No  | No              |
|                              |                                                            |    | Peptic ulcer haemorrhage             | NA | No  | No              |
|                              |                                                            |    | Rectal haemorrhage                   | NA | No  | No              |
|                              |                                                            |    | Ulcer haemorrhage                    | NA | No  | No              |
|                              | Gastrointestinal perforation (narrow)                      | NA | Abdominal abscess                    | NA | No  | No              |
|                              |                                                            |    | Duodenal ulcer perforation           | NA | Yes | No              |
|                              |                                                            |    | Gastric perforation                  | NA | Yes | No              |
|                              |                                                            |    | Infectious peritonitis               | NA | Yes | No              |
|                              |                                                            |    | Intestinal perforation               | NA | Yes | No              |
|                              |                                                            |    | Peptic ulcer perforation             | NA | Yes | No              |

|                                           |                                                                                            |                                               |                                      |    |     |     |
|-------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------|----|-----|-----|
| Hepatotoxicity <sup>e</sup>               | Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow) | NA                                            | Ascites                              | NA | Yes | No  |
|                                           |                                                                                            |                                               | Asterixis                            | NA | Yes | No  |
|                                           |                                                                                            |                                               | Hepatic failure                      | NA | Yes | No  |
|                                           |                                                                                            |                                               | Hepatic necrosis                     | NA | Yes | No  |
|                                           |                                                                                            |                                               | Hepatic steatosis                    | NA | No  | Yes |
|                                           |                                                                                            |                                               | Hepatocellular injury                | NA | No  | No  |
|                                           |                                                                                            |                                               | Hepatotoxicity                       | NA | No  | No  |
|                                           | Hepatitis, non-infectious (narrow)                                                         | NA                                            | Hepatitis                            | NA | No  | No  |
|                                           |                                                                                            |                                               | Hepatitis acute                      | NA | No  | No  |
|                                           |                                                                                            |                                               | Hepatitis cholestatic                | NA | No  | No  |
|                                           |                                                                                            |                                               | Hepatitis toxic                      | NA | No  | No  |
|                                           | NA                                                                                         | NA                                            | Blood bilirubin increased            | NA | No  | No  |
|                                           |                                                                                            |                                               | Hepatic enzyme abnormal              | NA | No  | No  |
|                                           |                                                                                            |                                               | Hepatic enzyme increased             | NA | No  | No  |
|                                           |                                                                                            |                                               | Hypertransaminasaemia                | NA | No  | No  |
|                                           |                                                                                            |                                               | Liver function test abnormal         | NA | No  | No  |
|                                           |                                                                                            |                                               | Transaminases increased              | NA | No  | No  |
|                                           | NA                                                                                         | At least 2 of 3 terms required on same report | Alanine aminotransferase increased   | NA | No  | No  |
|                                           |                                                                                            |                                               | Aspartate aminotransferase increased | NA | No  | No  |
|                                           |                                                                                            |                                               | Gamma-glutamyltransferase increased  | NA | No  | No  |
| Osteonecrosis                             | NA                                                                                         | NA                                            | Osteonecrosis                        | NA | No  | Yes |
| Pancreatitis                              | Acute pancreatitis (broad)                                                                 | A or (B and C)                                | Pancreatitis                         | A  | No  | No  |
|                                           |                                                                                            |                                               | Pancreatitis acute                   | A  | No  | No  |
|                                           |                                                                                            |                                               | Pancreatitis necrotising             | A  | Yes | No  |
|                                           |                                                                                            |                                               | Blood amylase increased              | B  | No  | No  |
|                                           |                                                                                            |                                               | Lipase increased                     | B  | No  | No  |
|                                           |                                                                                            |                                               | Abdominal pain                       | C  | No  | No  |
|                                           |                                                                                            |                                               | Abdominal pain upper                 | C  | No  | No  |
|                                           |                                                                                            |                                               | Abdominal tenderness                 | C  | No  | No  |
|                                           |                                                                                            |                                               | Acute abdomen                        | C  | No  | No  |
|                                           |                                                                                            |                                               | Ascites                              | C  | No  | No  |
|                                           |                                                                                            |                                               | Fat necrosis                         | C  | No  | No  |
|                                           |                                                                                            |                                               | Ileus paralytic                      | C  | No  | No  |
| Ventricular arrhythmia and cardiac arrest | Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (narrow)      | NA                                            | Acute left ventricular failure       | NA | Yes | No  |
|                                           |                                                                                            |                                               | Adams-Stokes syndrome                | NA | Yes | No  |
|                                           |                                                                                            |                                               | Cardiac arrest                       | NA | Yes | No  |
|                                           |                                                                                            |                                               | Cardio-respiratory arrest            | NA | Yes | No  |
|                                           |                                                                                            |                                               | Circulatory collapse                 | NA | Yes | No  |
|                                           |                                                                                            |                                               | Pulse absent                         | NA | Yes | No  |
|                                           |                                                                                            |                                               | Shock                                | NA | Yes | No  |
|                                           |                                                                                            |                                               | Ventricular fibrillation             | NA | Yes | No  |
|                                           | Ventricular tachyarrhythmias (broad)                                                       | NA                                            | Torsade de pointes                   | NA | No  | No  |
|                                           |                                                                                            |                                               | Ventricular arrhythmia               | NA | No  | No  |
|                                           |                                                                                            |                                               | Ventricular extrasystoles            | NA | No  | No  |
|                                           |                                                                                            |                                               | Ventricular fibrillation             | NA | Yes | No  |
|                                           |                                                                                            |                                               | Ventricular tachycardia              | NA | No  | No  |

|           |                                            |    |                                        |    |     |     |
|-----------|--------------------------------------------|----|----------------------------------------|----|-----|-----|
| Myopathy  | Rhabdomyolysis / myopathy (broad)          | NA | Blood creatine phosphokinase increased | NA | No  | No  |
|           |                                            |    | Muscle necrosis                        | NA | No  | Yes |
|           |                                            |    | Myopathy                               | NA | No  | Yes |
|           |                                            |    | Rhabdomyolysis                         | NA | Yes | No  |
| Seizures  | Convulsions (narrow)                       | NA | Convulsion                             | NA | No  | No  |
|           |                                            |    | Epilepsy                               | NA | No  | No  |
|           |                                            |    | Grand mal convulsion                   | NA | No  | No  |
|           |                                            |    | Status epilepticus                     | NA | Yes | No  |
| Psychosis | Psychosis and psychotic disorders (narrow) | NA | Delusion                               | NA | No  | No  |
|           |                                            |    | Hallucination                          | NA | No  | No  |
|           |                                            |    | Hallucination, auditory                | NA | No  | No  |
|           |                                            |    | Hallucination, tactile                 | NA | No  | No  |
|           |                                            |    | Hallucination, visual                  | NA | No  | No  |
|           |                                            |    | Hallucinations, mixed                  | NA | No  | No  |
|           |                                            |    | Illusion                               | NA | No  | No  |
|           |                                            |    | Paranoia                               | NA | No  | No  |
|           |                                            |    | Psychotic disorder                     | NA | No  | No  |
|           |                                            |    | Schizophreniform disorder              | NA | No  | No  |

<sup>a</sup> The MedDRA version used was 14.1.

<sup>b</sup> If applicable, the term category is used to algorithmically determine whether the adverse effect of interest is on a given report.

<sup>c</sup> Life-threatening reactions and persistent disabilities are two of the possible serious outcomes considered in this benefit-risk assessment. Whether or not there is a term on a report that implies either of these outcomes for a certain adverse effect is one of the criteria considered when assigning serious outcomes to reported adverse effects; for a complete description, see Additional file 2.

<sup>d</sup> This term was interpreted as describing a reaction whereby the drug caused an acute and reversible worsening of a pre-existing condition; therefore it was not considered to intrinsically imply persistent diabetes as caused by the drug.

<sup>e</sup> Terms that relate to chronic liver injury have actively been excluded.