

A.N.R.S

ANRS scale to grade the severity of adverse events in adults

Version n° 1.0 4 November 2008

(Translation of the French version n°6 9 September 2003)

This severity scale is a working guide intended to harmonise evaluation and grading practices for symptomatology in ANRS biomedical research protocols.

In practice, the items evaluated are grouped according to the system taking the form of a non-exhaustive symptomatic table (and not a classification of pathologies). Our choices focus on the most frequently observed clinical and biological signs or those whose monitoring is essential to ensure the protection of the subjects participating in the research.

For abnormalities NOT found elsewhere on the Table, refer to the scale below to estimate grade of severity:

GRADE 1	<i>Mild</i>	Mild or transient discomfort, without limitation of normal daily activities; no medical intervention or corrective treatment required.
GRADE 2	<i>Moderate</i>	Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.
GRADE 3	<i>Severe</i>	Marked limitation of normal daily activities; medical intervention and corrective treatment required, possible hospitalisation.
GRADE 4	<i>Life-threatening</i>	Severe limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting.

Abbreviations used in the table:

ULN	: Upper Limit of Normal
RBC	: Red Blood Cells
FEV1	: Forced Expiratory Volume in one second
EMG	: Electromyogram
Prothrombin Time (%)	: Corresponds to Quick time (sec)
aPTT	: activated Partial Thromboplastin Time

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Please note that this scale was devised for use in HIV, HCV or HBV related pathologies.

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GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
HAEMATOLOGY					
1	Haemoglobin (g/dl)	8.0 – 9.4	7.0 – 7.99	6.5 – 6.99	< 6.5
2	Leucocytes (/mm ³)	3 000 – 3 900	2 000 – 2 999	1 000 – 1 999	< 1 000
3	Neutrophils (/mm ³)	1 000 – 1 500	750 – 999	500 – 749	< 500
4	Platelets (/mm ³)	75 000 – 99 000	50 000 – 74 999	20 000 – 49 999	<20 000 or generalized petechiae
5	Prothrombin Time (%)	/	45 – ≤ 70	20 – < 45	< 20
6	aPTT	1.0 – 1.66 x ULN	> 1.66 – 2.33 x ULN	> 2.33 – 3.0 x ULN	> 3.0 x ULN
BIOCHEMISTRY					
<i>Hepatic and pancreatic biochemistry</i>					
7	AST (SGOT) (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
8	ALT (SGPT) (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
9	GAMMA GT (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
10	Alkaline phosphatase (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
11	Hyperbilirubinaemia (μmol/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0x ULN
12	Amylaseaemia (UI/l) / Lipasaemia (UI/l)/ Pancreatitis	≥1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 3.0 x ULN with acute abdominal pain and/or imaging indicating acute pancreatitis.	> 3.0 x ULN with abdominal pain and signs of shock.
13	CPK (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
<i>Lipid status</i>					
14	Hypertriglyceridaemia (mmol/l)	/	4.50 – 8.59	8.60 – 13.70	> 13.70
15	Hypercholesterolaemia (mmol/l)	>ULN –7.75	>7.75 – 10.34	>10.34 – 12.92	>12.92

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<i>Electrolytes / Evaluation of renal function / Metabolism</i>					
16	Hyponatraemia (mEq/l)	130 – 135	123 – 129	116 – 122	<116
17	Hypernatraemia (mEq/l)	146 – 150	151 – 157	158 – 165	>165
18	Hypokalaemia (mEq/l)	3.2 – 3.4	2.8 – 3.1	2.5 – 2.7	<2.5
19	Hyperkalaemia (mEq/l)	5.6 – 6.0	6.1 – 6.5	6.6 – 7.0	>7.0
20	Bicarbonate (mEq/l or mmol/l)	20.0 – 24.0	15.0 – 19.99	10.0 – 14.99	< 10.0
21	Creatininaemia (µmol/l)	1.0 – 1.50 x ULN	> 1.50 – 3.0 x ULN	> 3.0 – 6.0 x ULN	6.0 x ULN or dialysis required
22	Blood Urea Nitrogen (UI/l)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
23	Hypocalcaemia (mmol/l)	1.95 – 2.10	1.75 – 1.94	1.50 – 1.74	< 1.50
24	Hypercalcaemia (mmol/l)	2.65 – 2.87	2.88 – 3.13	3.14 – 3.38	> 3.38
25	Hypophosphataemia (mg/dl)	2.0 – 2.4	1.5 – 1.9	1.0 – 1.4	<1.0
26	Hyperuricaemia (µmol/l)	1.25 – 2.0 x ULN	> 2.0 – 5.0 x ULN	> 5.0 – 10.0 x ULN	> 10.0 x ULN
27	Hypoglycaemia (mmol/l)	3.1 – 3.6	2.2 – 3.0	1.7 – 2.1	< 1.7
28	Hyperglycaemia (mmol/l)	6.1 – 7.0	> 7.0 – 16.5	> 16.5 without ketosis.	See diabetes Item no. 52 (grade 4)
29	Hyperlactataemia (mmol/l) (venous blood sample)	2.0 – 2.99*	3.0 – 3.99**	4.0 – 4.99**	≥ 5.0***
<i>Urinalysis</i>					
30	Proteinuria (dipstick)	+	++	≥ +++	Nephrotic syndrome
31	Haematuria.	≥ 80 RBC/µl (dipstick).	≥ 200 RBC/µl (dipstick).	Macroscopic with or without clots.	Obstructive or requiring a blood transfusion.

* Lactataemia – GRADE 1: a confirmatory test is necessary within 8 to 10 days

** Lactataemia – GRADE 2, 3: a confirmatory test is necessary within 24 hours.

*** Lactataemia – GRADE 4: a confirmation test is necessary immediately.

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<i>Gastro-intestinal/hepatic/pancreatic abnormalities</i>					
32	Nausea.	Transient, normal diet.	Restricted diet for less than 3 days.	Restricted diet for more than 3 days.	Liquid only diet. Hospitalization required.
33	Vomiting.	Transient: 2 – 3 episodes / day or duration ≤ 1 week.	Repeated: 4 – 5 episodes / day or duration > 1 week.	Solid/liquid vomiting for 24 h. Orthostatic hypotension. Perfusion required.	Hospitalization for hypovolemic shock.
34	Diarrhoea.	Transient, 3 – 4 stools / day, diarrhoea ≤ 1 week.	Persistent, 5-7 stools / day, diarrhoea > 1 week.	> 7 stools/day or requiring perfusion. Bloody stools.	Hospitalization, Hypovolemic shock, perfusion.
35	Constipation.	/	Moderate abdominal pain, 78 h without stools. Treatment required.	Meteorism. Requiring disimpaction or hospital treatment.	Meteorism with vomiting or occlusion.
36	Dysphagia.	Mild discomfort when swallowing.	Difficulty in swallowing but food intake possible.	Inability to swallow solids.	Inability to swallow liquids, perfusion required.
37	Oesophagitis.	Pyrosis occurring less than once a week	Pyrosis occurring at least once a week but relieved by PPIs*	Pyrosis occurring at least once a week but not relieved by PPIs*	Food intolerance and vomiting

*PPIs: proton pump inhibitors

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<i>Respiratory abnormalities</i>					
38	Bronchospasm.	Transient, no treatment, FEV1 70 % - < 80 %.	Permanent, Improvement under bronchodilation FEV1 50 % - < 70 %.	Persistent under bronchodilation. FEV1 25 % - < 50 %.	Cyanosis, FEV1 < 25 % intubation.
39	Dyspnoea	Dyspnoea upon exertion.	Dyspnoea during normal daily activities.	Dyspnoea at rest.	Dyspnoea requiring respiratory assistance.
<i>Muscular abnormalities</i>					
40	Myalgia (excluding injection site).	Mild myalgia for less than 4 weeks. Not requiring analgesic treatment.	<p><i>Presence of one of the following symptoms:</i></p> <p>1 – Mild to moderate myalgia for more than 4 weeks and/or which may require treatment with level 1* analgesics.</p> <p>2 – Predominance of difficulties upon exertion (difficulty in climbing stairs or rising from a sitting position). Can walk without assistance. Optional confirmation through the identification of biological (CPK), electromyographical (EMG) or histological (muscular biopsy) abnormalities.</p>	<p><i>Presence of one of the following symptoms:</i></p> <p>1 – Moderate to severe myalgia for more than 4 weeks requiring treatment with level I/II* analgesics.</p> <p>2 – Assistance required for walking and normal daily activities.</p> <p>Paraclinical confirmation recommended (CPK, EMG and/or muscular biopsy).</p>	<p><i>Presence of one of the following symptoms:</i></p> <p>1 – Severe myalgia not related to exertion requiring treatment with level II/III* analgesics.</p> <p>2 – Muscular weakness making walking impossible without assistance.</p> <p>3 – Acute rhabdomyolysis with muscular necrosis and oedema.</p> <p>4 – Acute rhabdomyolysis with electrolytic disturbances and renal insufficiency. Paraclinical confirmation required (biology, EMG and/or muscular biopsy).</p>

* Level I analgesics
 * Level II analgesics
 * Level III analgesics

: Peripheral analgesics (paracetamol and/or salicylics or non-steroid anti-inflammatory drugs) ;
 : Weak opiates (codeine, dextropropoxyphene), morphinic agonists-antagonists (buprenorphine, nalbuphine) ;
 : Morphine.

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<i>Cardiovascular abnormalities</i>					
41	Arterial hypertension.	Transient or permanent. Increased blood pressure \leq 20 mmHg and systolic BP 140-159 or diastolic BP 90-99.	Permanent. Increased blood pressure $>$ 20 mmHg and systolic BP 160-179 or diastolic BP 100-109.	Permanent. Systolic BP \geq 180 or diastolic BP $>$ 110	Malignant or accelerated arterial hypertension.
42	Orthostatic hypotension.	Decreased systolic blood pressure \leq 20 mmHg in orthostatic position. No treatment.	Decreased systolic blood pressure $>$ 20 mmHg, durable but corrected with liquid intake per os.	Perfusion required.	Hypovolemic shock requiring hospitalization.
43	Ventricular cardiac rhythm disorders.	/	Isolated ventricular extrasystoles, no treatment, symptomatic or asymptomatic.	Recurrent, persistent or symptomatic cardiac rhythm disorders. Treatment required.	Dysrhythmia requiring hospitalization.
44	Prolongation of the QT interval.	/	Man: $>$ 450 and $<$ 500 ms Woman: $>$ 470 and $<$ 500 ms	$>$ 500ms	$>$ 500 ms with clinical symptoms (ventricular rhythm disorders, syncope, torsade de pointes)
45	Cardiac ischaemia.	/	Atypical pain under exploration.	Appearance of angina upon exertion, controlled with treatment.	Myocardial infarction, unstable angina, preinfarction syndrome.
46	Pericarditis.	Chance discovery of a small effusion during ultrasound scan	Moderate effusion with few symptoms. No treatment or intervention deemed necessary for the time being.	Moderate or significant symptomatic effusion but without tamponade. Treatment required and hospitalization to be considered.	Tamponade. Hospitalization and intervention required.
47	Stroke.	/	/	Transient Ischemic Attack (regressive focal neurological syndrome within 24 h).	Cerebrovascular accident non-regressive within 24 h.
48	Peripheral arterial embolism.	/	/	/	Peripheral arterial embolism. Hospitalization. Adapted treatment.
49	Deep vein thrombosis and/or pulmonary embolism.	/	/	Deep vein thrombosis. Anticoagulant treatment. Hospitalization to be considered.	Pulmonary embolism. Adequate hospitalization and treatment.

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<i>Endocrine abnormalities</i>					
50	Hyperthyroidism.	Infraclinical hyperthyroidism. Low TSH. Normal free T3 and T4.	Moderate, non-complicated thyrotoxicosis. Treatment required.	Malignant exophthalmia. Cardiac arrhythmia. Myopathy.	Thyrotoxic crisis and/or cardiac insufficiency.
51	Hypothyroidism.	Infraclinical hypothyroidism. Increased TSH but <12 mU/l. Normal free T4.	Simple hypothyroidism without complications. Treatment required.	Severe hypothyroidism with multiple clinical symptoms. Urgent treatment. Hospitalization to be considered.	Myxoedematous coma.
52	Diabetes/hyperglycaemia.	Moderate fasting hyperglycaemia between 6.1 and 7 mmol/l. No immediate treatment required.	Fasting glycaemia: > 7 mmol/l. Special diet required, possibly supplemented with oral antidiabetics.	Fasting glycaemia:>16.5 mmol/l on an empty stomach, with or without clinical symptoms. Insulin therapy required.	Ketoacidosis or hyperosmolarity (>27.8 mmol/l without acidosis).
<i>Cutaneous abnormalities</i>					
53	Cutaneous and/or mucosal eruptions.	Erythaema, Moderate pruritis.	Extended maculopapular eruption, with or without pruritis.	Extended papulovesicular or oozing eruption. Palpable purpura (suggestive of vasculitis). Polymorphous erythaema. Small-size cutaneous or mucous ulcerations.	Any blistering cutaneous and/or mucosal lesions (Lyell or Stevens-Johnson). Febrile erythrodermia, whether or not associated with other signs indicative of hypersensitivity. Cutaneous necrosis requiring surgical excision.
54	Symptoms of immediate hypersensitivity, with or without cutaneous symptoms.	/	Acute localised urticaria.	Giant urticaria, Quincke's oedema.	Anaphylactic shock.

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<i>Neurological abnormalities</i>					
55	Wakefulness / sleep disorders.	Minor attention and concentration impairment.	Diurnal somnolence and/or difficulty falling asleep and/or night time awakening, mental activity decreased, obtundation.	Sleep-wake cycle modification or insomnia requiring treatment or change in dream content. Obvious confusional syndrome with temporal disorientation.	Sleep-wake cycle disorganisation not responding to treatment. Dreamlike confusional syndrome, coma and/or convulsion.
56	Psychiatric disorders.	Minor anxiety.	Anxiety requiring treatment or moderate depression.	Major anxiety or confirmed depressive episode requiring treatment.	Acute psychosis requiring hospitalization, including suicidal ideation, manic state, hallucinatory delusion.
57	Cephalalgia.	Intermittent, no treatment.	Requiring level I* analgesics.	Requiring at least level II* analgesics.	Not responsive to level III* analgesics.
58	Paraesthesia.	Paraesthesia, mild pain, no treatment.	Paresthesia, permanent pain of moderate intensity, requiring level I* analgesics.	Paraesthesia, permanent pain of severe intensity, requiring at least level II* analgesics.	Unbearable pain resulting in disability, restricted activity despite administration of level III* analgesics.
59	Motor deficiency.	Subjective feeling of weakness without objective impairment, no reflex changes.	Distal motor deficiency, moderate functional impairment or reflex changes.	Marked motor deficiency interfering with normal daily activities.	Confined to bed or a wheelchair because of motor deficiency.
60	Difficulty controlling movement.	Occasional clumsiness, mild coordination difficulties.	Tremor or dyskinesia or dysmetria, or dysarthria, moderate limitation of normal daily activities.	Upper or lower limbs ataxia or abnormal movements, limitation of normal daily activities.	Inability to stand up. Total dependence.
61	Sensory loss.	Mild sensory loss, regardless of mode and distribution (focal or symmetric).	Moderate sensory loss.	Severe sensory loss.	Extensive sensory loss involving the trunk and four limbs.

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* Level II analgesics
* Level III analgesics

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: Morphine.

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<i>Miscellaneous</i>					
62	Fever (oral temperature, °C) for more than 12 h.	37.7 – 38.9	39 – 39.5	39.6 – 40.5	> 40.5
63	Renal colic.	Spontaneous regression of symptoms. Pain not requiring treatment.	Colic requiring medical treatment.	Obstructive syndrome, does not disappear spontaneously.	/
64	Fatigue.	Normal daily activities reduced by less than 25% for less than 48 h.	Normal daily activities reduced by 25 – 50 % for more than 48 h.	Normal daily activities reduced by more than 50%, cannot work for more than 48 h.	Unable to care for self. Assistance required for normal daily activities.
65	Arthritis / Arthralgia.	Arthralgia.	Arthralgia, with or without articular effusion or with moderate functional impairment.	Marked arthritis with or without effusion or with severe functional impairment.	/
66	Ocular disorders.	Conjunctival hyperaemia.	Moderate pain. Conjunctivitis.	Decreased visual acuity. Uveitis. Severe pain. Glaucoma.	/

ANRS vaccine trials.

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1	Erythaema, oedema, nodule (induration).	< 15 x 15 cm.	≥ 15 x 15 cm.	Ulceration or superinfection or superficial phlebitis.	Skin necrosis
2	Pain, functional impairment.	Mild, no limitation of movements.	Pain inducing partial mobility impairment.	Pain inducing functional impotence.	/