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3 **Endpoints in pediatric pain studies**  
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## Introduction

### 1. Neurobiology of pediatric pain: essentials for drugs-related studies

The neonatal stage of life is characterized by high sensitivity to pain and great vulnerability to neuronal cell death [1]. Anecdotal reports have shown prolonged allodynia and hyperalgesia after pain and tissue damage within the first weeks of life, extending beyond the period associated with tissue healing [2-7]. For example, 4–6 months-old term infants who had undergone circumcision responded more intensely to immunization than did their uncircumcised peers [5]. On the other hand, children who had undergone major surgery in combination with preemptive analgesia within the first months of life did at 14 and 45 months of age not show different behavioural pain responses and saliva cortisol concentrations when exposed to vaccinations compared to age matched controls. [8]. Thus, the question is whether preemptive administration of analgesics indeed prevents from possible long-term consequences of neonatal pain. There are some clues from animal experiments. Neonatal nerve ligation in rodents led to long-term hyperalgesia, which was not attenuated when local anesthetics were administered [9]. Neonatal exposure to carrageen or Freud adjuvants CFA led to hyposensitivity or no alterations, but to hypersensitivity when adult animals were re-exposed to inflammatory pain [10-14]. In contrast, formalin injections or laparotomy in newborn rats led to thermal hyposensitivity at adult age [13-15], which was attenuated by morphine administration [15].

Tissue damage and neonatal pain disturb normal development of the nociceptive neural circuits, as expressed by structural and functional neuroanatomical changes both peripherally [9, 16] [17] and at spinal cord level [11, 18]. Moreover, changes in spinal gene expression involved in the transmission of nociception have been documented [13]. These animal experiments may provide an explanation for the long-term effects found in human children.

In summary, we do not know whether adequate analgesia prevents the development of long-term alterations in pain sensitivity. And, if alterations occur, will they be restricted to the dermatome of tissue injury (spinal changes) or be generalized all over the body (supraspinal changes) [4].

Exposing neonates to pain or tissue damage is developmentally inappropriate and analgesics may not prevent them from developing subsequent pain hypersensitivity. A next question is whether this pain

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3 hypersensitivity will still exist 15 years after tissue injury or has recovered or reverted to  
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5 hyposensitivity. The few studies on this issue provide no or little information of the total analgesic  
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7 dosages during hospital stay [19, 20]. It would seem, therefore, that we need to perform more  
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9 randomized controlled analgesic trials (RCT) in children and perform follow-up studies in these same  
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11 patients through childhood and adolescence to gain insight in the long term effects of neonatal pain  
12  
13 and neonatal analgesia.  
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### 15 16 **Endpoints in clinical trials**

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18 A clinical trial endpoint is a measure that allows us to decide whether the null hypothesis of a clinical  
19  
20 trial should be accepted or rejected [21]. Possible endpoints in pediatric analgesic trials are: pain  
21  
22 intensity, time to first (rescue) analgesia, total analgesic consumption, adverse effects and long term  
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24 effects [22, 23]. RCTs may have more than one endpoint, in which case it is customary to differentiate  
25  
26 between primary and secondary outcomes.  
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28  
29 Assessing pain intensity in (preverbal) children is more difficult than in adults. Adults' self report of  
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31 pain is generally accepted as the gold standard (ref IASP) of pain assessment. The discussion merely  
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33 limits itself to the question which of the available self report scales is most appropriate in a given  
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35 situation. Pain intensity in young children can be assessed with validated observational pain  
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37 assessment instruments or multidimensional pain assessment instruments that include both behavioural  
38  
39 and physiological parameters. Self report is feasible from the age of 4 to 5 years. Because  
40  
41 observational pain instruments provide subjective outcomes, it is crucial that observers are well trained  
42  
43 and that interrater reliability has been tested and proven good. Establishing cutoff points that  
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45 differentiate between different levels of pain intensity is an important requirement, because rescue  
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47 medication is given when scores exceed specific values.  
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51 An important reference article is the one from the Pediatric Initiative on Methods, Measurement, and  
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53 Pain Assessment in Clinical Trials (Ped-IMMPACT), in which core domains and measures for clinical  
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55 pain trials have been defined [22].  
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59 The type of outcome measure also depends on the type of pain under study. Physiological parameters,  
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for example, are more promising for acute painful procedures such as heel lances or venipunctures

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3 than for chronic pain. In the next paragraph the different types of endpoints will be presented with a  
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5 focus on postoperative pain.  
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8 *1. Endpoint Pain intensity:*

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10 *a. Behavioral assessments*

11 The International Association for the Study of Pain (IASP) underlines that the inability to  
12 communicate verbally does not negate the possibility that an individual is experiencing pain and is in  
13 need of appropriate pain-relieving treatment [24]. Based on this note, behavioral-based pain  
14 observation instruments have been developed. The Children's Hospital Eastern Ontario Pain Scale  
15 (CHEOPS) [22, 25], and the Faces, Legs, Arms, Cry and Consolability (FLACC) [26, 27] have been  
16 validated for postoperative pain in 1 to 7-year-old children. The COMFORT-behavior scale has been  
17 validated to that aim in 0 to 3-year-old children in the intensive care setting [28]. These scales have  
18 several items in common; facial expression, cry and body movements.  
19

20 Children with severe intellectual disabilities may show idiosyncratic behavior when they are in pain. It  
21 may be advised against, therefore, to apply pain scales developed for children without intellectual  
22 disabilities to these children [29, 30]. At least four validated postoperative pain instruments for  
23 children with intellectual disabilities have been developed. One is the revised FLACC, which allows  
24 for individualized behavior added to each of the 5 items of the scale. It has been validated for  
25 postoperative pain [31] and proved to have a high degree of clinical utility [32]. The second scale is  
26 the Paediatric Pain Profile (PPP), a 20-item scale that has been validated for postoperative pain [33,  
27 34]. The PPP consists of three sets of recordings: two retrospective parent ratings of the child's  
28 behaviour – i.e. when the child was at his or her best and during painful episodes – and a prospective  
29 rating by the nurse, e.g. postoperatively. Although completing the PPP may take up more time than the  
30 FLACC, it may be well worthwhile for research purposes. The third scale is the non-communicating  
31 children's pain checklist (NCCPC) [35] of which the postoperative version (NCCPC-PV) [36]  
32 includes 27 items and requires a 10 minutes observation. A fourth scale is the Checklist Pain  
33 Behaviour (CPB), which has been validated for postoperative pain and reduced without loss of  
34 information to a 10 item version [37, 38]. In addition, a recent study described the use of an  
35 individualized Numeric Rating Scale based solely on the child's individual pain indicators as  
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3 described by parents and caregivers [39]. The psychometric properties of this scale are promising;  
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5 nevertheless, the essential involvement of the parents may be a drawback especially when the scale is  
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7 used for research purposes [40].  
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10 *b. Self report*

11 Examples of self report tools for 2 to 3 year old toddlers are the Poker Chip Tool [41] and the Faces  
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13 Pain Scale-Revised, recommended for research purposes in over 4-year-olds [42, 43]. The Numeric  
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15 Rating Scale pain (NRS-11) [44] and Visual Analogue Scale pain (VAS) [45] should preferably not  
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17 be used in children below the age of 8 years because it requires a certain cognitive level of  
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19 development to translate pain intensity into numbers or distances on a 10 cm ruler. The Poker Chip  
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21 Tool, Faces Pain Scale-revised and VAS have also been suggested by the Pediatric Initiative on  
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23 Methods, Measurements and Pain Assessment in Clinical Trials (PedIMMPACT) and also came up as  
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25 valid in two reviews [22] [43, 46].  
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30 *c. Physiological parameters*

31 As behavior-based assessment instruments remain subjective, researchers continue to search for  
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33 neurobiological-based and more 'objective' parameters of pain intensity [47]. Several instruments  
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35 indeed go some way in this direction by including physiological items as well, such as the PIPP and  
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37 the COMFORT scale [48, 49]. However, heart rate and blood pressure proved not been sensitive  
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39 enough for postoperative pain assessment, probably because treatment, blood loss, fever and other  
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41 conditions will influence these parameters, [50, 51].  
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44 New methods, such as near-infrared spectroscopy (NIRS) and skin conductance, may help to objectify  
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46 pain or stress in nonverbal humans.  
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48 NIRS measures regional changes in oxygenated and deoxygenated hemoglobin concentration. The  
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50 technique is based on the assumption that increased tissue oxygenation represents a greater regional  
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52 cerebral blood flow. This, in its turn, is associated with higher neuronal activity as seen in noxious  
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54 events (encoded by frequency of firing and number of activated neurons)[52]. The use of NIRS in  
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56 pediatrics has been limited to acute pain in neonates [53-55]. One study compared NIRS  
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58 measurements during 33 heel lance procedures in 12 stable newborns with facial expression. Brain  
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60 activity in most of the newborns was related to facial expression. Some newborns did not show a

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3 change in facial expression, however, although NIRS readings revealed increased cortical activity  
4 during the procedure [54].  
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7 The measurement of stress by skin conductance is based on neurophysiologic arousal with increased  
8 activity in the sympathetic nervous system, leading to sweating in the palms of the hand and the foot  
9 soles. The level of increase may serve as a surrogate measure of stress and not of pain per se [56].  
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#### 12 13 *d. Biomarkers*

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15 Hormonal stress markers such as salivary cortisol and (nor) epinephrine may have additional value in  
16 the context of analgesia trials [57]. Nevertheless, because stress and pain are correlated but difficult to  
17 distinguish, these hormone levels should not be considered as primary endpoints of pain studies. Age-  
18 dependent differences in hormonal levels as well as age-dependent differences in circadian rhythm are  
19 important confounders. Especially in postoperative patients the extent and duration of the so-called  
20 hormonal stress response are highly determined by age [57] However, salivary cortisol could be a  
21 substitute marker for pain or stress in severely cognitively impaired children. Remarkably, RCTs in  
22 this vulnerable patient group have not yet been performed despite the fact that co-medication, such as  
23 anticonvulsants, could influence opioid use during surgery, as reported in a single study from 1990,  
24 which so far has never been replicated [58].  
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#### 40 41 *e. Brain activity related parameters*

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43 Experimental approaches involving the use of fMRI and PET scans have been tested in the research  
44 setting only [59, 60]. PET scans performed solely for pediatric research reasons may, however, meet  
45 with ethical and practical obstacles as they involve administration of radioactive labeled drugs. As a  
46 non invasive procedure, fMRI is more promising for (semi)clinical evaluation and can be combined  
47 with quantitative sensory testing [61].  
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52 Neurophysiological measurements such as EEG and somatosensory response have so far not identified  
53 a specific pain signal that could be useful in daily clinical practice. There is direct EEG evidence of  
54 specific noxious-evoked neural activity in the infant brain [62]. Somato-sensory responses have been  
55 demonstrated in young infants but as yet cannot serve as endpoints; we first need to establish normal  
56 values of voltage, frequency and duration.  
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3 *f. Time to first (rescue) analgesia and analgesic consumption*  
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5 As many postoperative patients will receive preemptive analgesic drugs, time to first rescue analgesia  
6 may serve as a clinical endpoint together with the total analgesic consumption over the first 12, 24 or  
7 48 hours. Consumption should be expressed in microgram or mg per kg per hour or per 24 hours so as  
8 to enable comparison. Ideally these endpoints should be combined with scores obtained from validated  
9 pain assessment instruments.  
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16 *g. Safety/adverse effects*  
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18 Documentation of drug safety is highly important, especially in pediatric drug trials. There is some  
19 debate on whether it is better to have a pre-defined list of possible adverse events to be taken into  
20 account, or to resort to an unstructured approach in which researchers, parents or other individuals  
21 report any suspected adverse events [22]. This latter approach may carry the risk of underreporting of  
22 adverse events.  
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29 Safe and effective pain treatment in neonates and young infants requires thorough understanding of  
30 various developmental aspects of drug disposition and metabolism. In general, the phenotypic  
31 variation in drug disposition and metabolism is based on constitutional, genetic and environmental  
32 factors. The clearance rate of most drugs is lower in neonates than in adults and older children.  
33 Neonates still show immature renal function, i.e. decreased glomerular filtration rate and less effective  
34 tubular reabsorption and/or excretion. Moreover, they have a lower capacity of drug metabolizing  
35 enzymes (39-44). Furthermore, as reviewed by both Weinshillboum (45) and Evans and McLeod (46),  
36 the disposition and action of many drugs are polygenetic determined events. Polymorphisms in drug  
37 metabolizing enzymes, transporters and receptors determine to a larger extent the spectrum of drug  
38 response (i.e., ranging from no effect to drug toxicity).  
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51 *h. Long-term effects of analgesic treatment*  
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53 The short and long-term consequences of prolonged opioid use in newborns and infants are largely  
54 unknown. Studies in animals suggest potential adverse long term effects of morphine. Morphine  
55 administration to neonatal rats produces long-term changes in behavior and brain function [63] and  
56 impairs the adult cognitive functioning [64], in particular spatial recognition memory [65]. Basic  
57 science has shown that the opioid system modulates neural proliferation in vivo[66]. Thus, it may well  
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3 be that morphine treatment harms the neurogenesis of newborn babies. Mechanistically, morphine  
4 induces apoptosis of human microglial cells [67] and stimulates red neuron degeneration in the rat  
5 brain, which may lead to cerebral dysfunction [68]. Boasen et al recently showed in rodents that either  
6 neonatal stress and morphine treatment produced long-lasting behavioral effects to a degree sufficient  
7 to alter learning, while the combination of neonatal stress and morphine did not [69].

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10 Endpoints in human studies should therefore include cognition, neuropsychological tests, a chronic  
11 pain questionnaire, and pain and detection thresholds. The latter thresholds may be assessed with  
12 quantitative sensory testing (QST), for which normal values are available [70].

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22 Finally, we should realize behavioral assessment instruments reveal other aspects of the phenomenon  
23 pain than do neurophysiological evaluation or the use of biomarkers. Moreover, no single parameter  
24 covers the whole spectrum from a nociceptive stimulus to behavior. It would seem essential, therefore,  
25 to also evaluate the fate of drugs in the body (pharmacokinetics) as well as the response of the body  
26 (pharmacodynamics).

### 27 *Pharmacokinetics of the parent drug and (active) metabolites in relation to pharmacodynamics.*

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It has become easier to measure plasma levels of drugs in children. Sophisticated analytical methods  
(e.g. LC-MS-MS) and statistical analyses (e.g. population pharmacokinetics-pharmacodynamics, such  
as NONMEM) require smaller and fewer samples [71]. A possible relationship between therapeutic  
plasma ranges and pharmacodynamic parameters has not yet been found. Mutation analysis can  
provide answers to individual aberrant responses although tailoring of analgesic dosing is still a long  
way to go [72].

Efforts to improve pain therapy, for example by means of RCTs, should be developed within the  
context of regulatory initiatives. American legislation ('Food and Drug Administration Modernization  
Act' in 1997, 'Best Pharmaceuticals for Children Act' in 2002 and 'Pediatric Research Equity Act' in  
2003) has come into force to promote drug development and authorization of medicines for use in  
pediatric patients. Similar legislation was introduced in the European Union in January 2007 ('The  
Pediatric Regulation') (Full text on [www.fda.gov](http://www.fda.gov) and [www.emea.europa.eu](http://www.emea.europa.eu)). These legislations and

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3 clinical trial registers (<http://clinicaltrials.gov>) provide essential information on ongoing studies in  
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5 other centers and prevent duplication of studies in this vulnerable age group.  
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10 *In summary*

11 Tools to measure pain are being used as primary endpoints in studies on the effects of analgesic drugs.  
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13 Nevertheless, further research is needed to develop more objective pain measurements, to identify  
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15 causes of variation in pain intensity and responses to pain treatment (both non-pharmacological and  
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17 pharmacological PK-PD), and to develop age and disease specific pain treatment protocols.  
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23  
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27  
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