TECHNICAL ANNEX

Supporting information for a Canadian Paediatric Society position statement

Guidelines for detection and management of hyperbilirubinemia in term and late preterm newborns (≥35 weeks gestational age)[1]

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METHOD OF STATEMENT DEVELOPMENT

A search of MEDLINE, including Epubs ahead of print, in-process, and other non-indexed citations (1946 to September 1, 2023), Embase (1974 to September 1, 2023), and the Cochrane Central Register of Controlled Trials (September 1, 2023) was performed, using the OVID interface. Search terms included: 'Hyperbilirubinemia', 'jaundice, neonatal', 'bilirubin', 'kernicterus', 'hemolysis', 'neonatal screening', 'phototherapy', 'exchange transfusion, whole blood', and 'transcutaneous bilirubinometry'. Reference lists of publications and guidelines were reviewed. All relevant Cochrane reviews were included. The hierarchy of evidence from the Centre for Evidence-Based Medicine (CEBM) (Oxford Centre for Evidence-Based Medicine 2014: http://www.cebm.net) was applied to the publications identified. Recommendations are based on the format by Shekelle *et al* [1].

TYPES OF PHOTOTHERAPY DEVICES

Phototherapy is an effective treatment in reducing TSB levels, need for blood exchange transfusion (BET) and bilirubin neurotoxicity [2][3]. Light in the blue green spectrum (wavelength around 475 nm) from the phototherapy lights leads to conformational changes in bilirubin, rendering it water soluble for excretion in the urine or bile [4][5]. Provision of phototherapy may be achieved via various types of light source: fluorescent tubes, halogen spotlights, light emitting diode (LED), and fiberoptic lights [4]. LED phototherapy systems may be ideal as they are power efficient, have long-lasting uniform irradiance, run quietly, can be portable, and are generally less heat producing [6]. Intensive phototherapy with optimal irradiance can be achieved using blue LED lights and may be more effective than other types of light source in reducing TSB [5][7][8]. Pads and blankets use flexible optic fibers connected to a light source such as LED [5]. While not as effective as other light-emitting devices in reducing TSB due to indirect light source exposure, they allow close contact of the fiberoptic pad or blanket to the skin surface [6][9][10], such that they can be used concomitantly with other types of phototherapy and allow breastfeeding and skin-to-skin care to continue without interruption of phototherapy.

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HOME PHOTOTHERAPY

A comprehensive home phototherapy program where selected low risk infants with mild hyperbilirubinemia can be considered for receiving phototherapy at home, based on clinical criteria such as those listed in **Table S1**. However, the success of such program is completely contingent upon the adequacy of community ancillary resources including lactation support, nursing care, medical care, access to phototherapy device that can be used at home and facility to perform blood sampling [11][12]. These infants must be checked daily, including testing for TSB levels during and after treatment. If the TSB continues to rise despite adequate home-phototherapy, or the TSB is ≥15 µmol/L above the phototherapy threshold, or the rate of rise is ≥5 µmol/L /hr. the infant should be readmitted to hospital for intensive phototherapy.

Table S1: criteria for consideration of home-phototherapy
▪ Birth at ≥38 weeks of gestational age ▪ At least 48 hours of post-natal life and did not yet receive phototherapy ▪ No hyperbilirubinemia neurotoxicity risk factor (Table 1b) ▪ Mild hyperbilirubinemia with TSB no more than 15µmol/L above the phototherapy threshold ▪ Clinically stable as determined by the care provider's assessment.

ADVERSE EFFECTS OF PHOTOTHERAPY

A recent systematic review of observational studies suggests that hyperbilirubinemia and phototherapy are associated with an increased risk of childhood asthma and other allergic diseases. However, it was not possible to discern the effect of hyperbilirubinemia versus phototherapy treatment in this association [13]. Another systematic review of a number of heterogenous observational studies suggests an association between phototherapy and the development of hemopoietic malignancies; however, as most of the studies were case control or retrospective cohort studies based on case registries, contributing potential confounders for development of malignancies could not have been accounted for, thus limiting the strength of association, especially given the age of diagnosis ranged from 1-29 years [14]. Lastly, two population-based studies suggest that phototherapy may be associated with a slightly increased risk of childhood seizure disorders [15][16].

THE NEW AND OLD PHOTOTHERAPY THRESHOLDS – A VISUAL COMPARISON

To understand how the new phototherapy thresholds deviate from previous guidelines, data from the 2007 CPS guidelines were extracted and superimposed to the new AAP phototherapy thresholds for a visual comparison. Phototherapy thresholds for infants with no risk factor were similar to those for low-risk infants in the CPS 2007 guidelines (**Comparison 1, figure S1a**). Phototherapy thresholds for infants with risk factors were similar to those for medium risk infants, but different from those for high-risk infants of the CPS 2007 guidelines (**Comparison 2, figure S1b**). Therefore, the only significant change from the previous phototherapy thresholds were a marginal increase in the phototherapy thresholds for infants that were considered in the previous statement to be at the highest risks for neurotoxicity (gestational age 35-37^{6} weeks and with risk factors). The new phototherapy thresholds are gestational age specific, and there is already a specific chart for the presence of risk factors. Therefore, the proposed changes in phototherapy thresholds should minimally affect how hyperbilirubinemia is

managed. **Comparison 3 (Figure S1c)** demonstrated that the subtraction of 30µmol/L to each of the data point from the previous statement's high-risk curve now closely approximate the new phototherapy thresholds for infants with risk factors. Therefore, in those infants with neurotoxicity risk factor(s), clinicians may choose to apply this "rule of 30" by initiating phototherapy at TSB ≤30 µmol/L of the new phototherapy threshold.

THE NEW AND OLD BET Thresholds – A VISUAL COMPARISON

To understand how the new exchange transfusion thresholds deviate from the previous guidelines, a similar visual comparison was performed using data from the 2007 CPS exchange transfusion thresholds superimposed to the thresholds of the new guideline. Exchange transfusion thresholds for infants with no risk factor were similar to those for low-risk infants in the CPS 2007 guidelines (**Comparison 4, figure S2a**). Exchange transfusion thresholds for infants with risk factors were similar to those for medium risk infants, but different from those for high-risk infants in the CPS 2007 guidelines (**Comparison 5, figure S2b**). The only significant change from the previous exchange transfusion thresholds were a marginal increase in the thresholds for infants that were considered in the previous statement to be at the highest risks for neurotoxicity (gestational age 35-37[6] weeks and with risk factors). The new phototherapy thresholds are gestational age specific, and there is already a specific chart for the presence of risk factors. Therefore, the proposed changes in exchange transfusion thresholds should minimally affect management. **Comparison 6 (Figure S2c)** showed that the addition of 30 µmol/L to each of the data point from the previous statement's high-risk curve will match with the new phototherapy thresholds for infants with risk factors. This "**rule of 30**" is simply the pre-exchange transfusion threshold as defined. At clinicians' discretion, BET can be initiated in these infants when the TSB is ≥30 µmol/L of the exchange transfusion threshold.

Figure S1a: Visual comparison 1. Phototherapy thresholds for infants with no risk factor

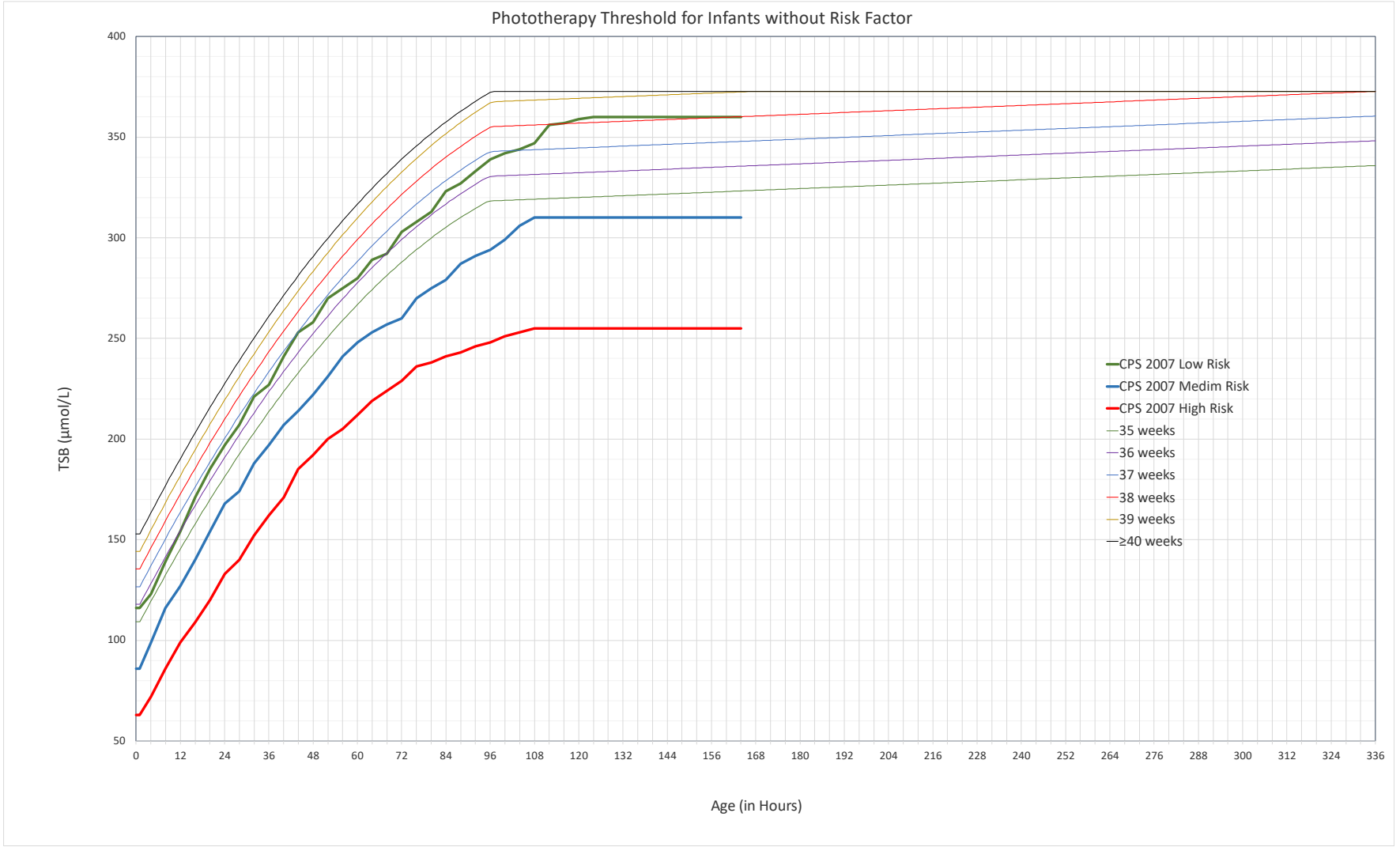


Figure S1b: Visual comparison 2. Phototherapy thresholds for infants with risk factor(s)

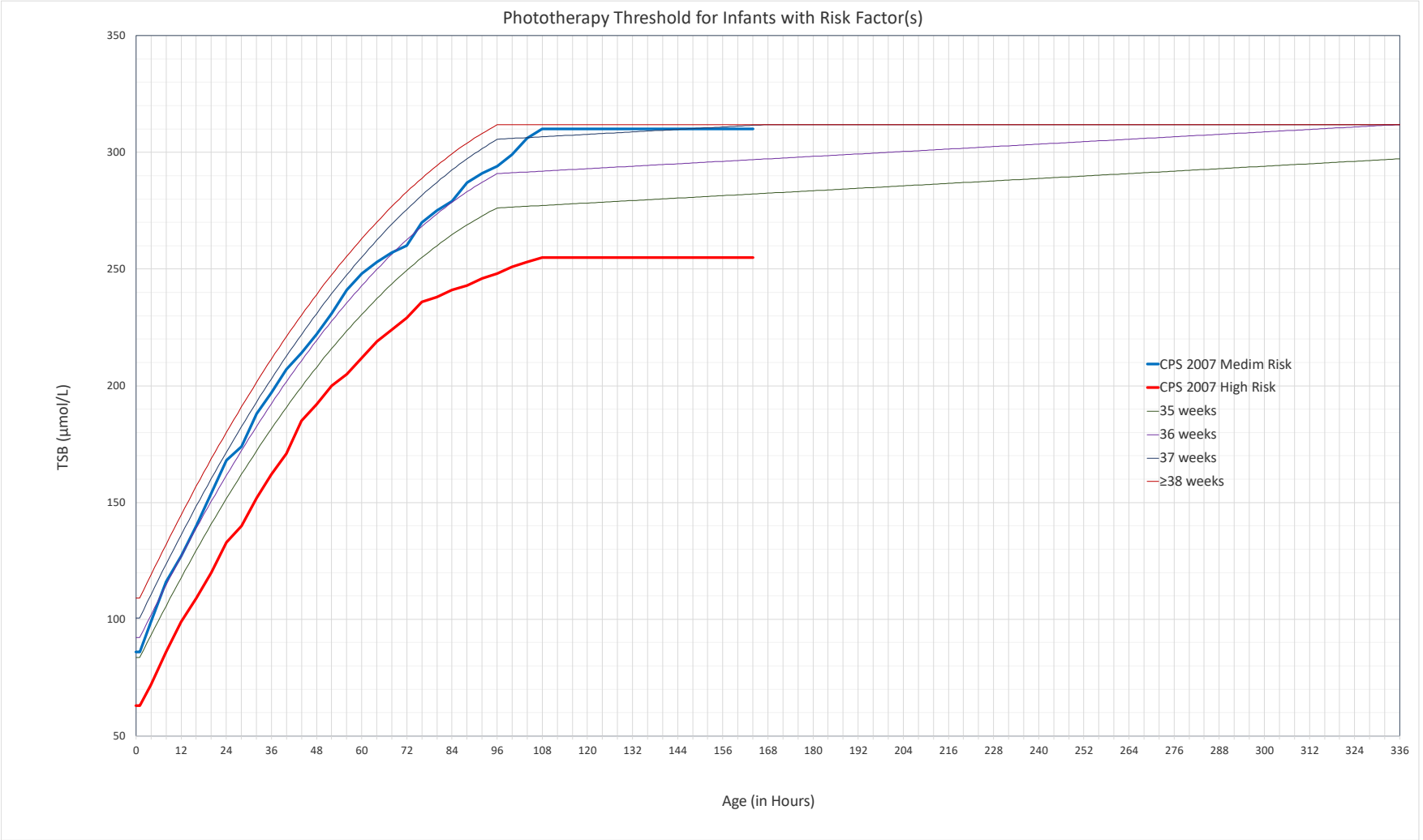


Figure S1c: Visual comparison 3. Phototherapy thresholds for infants with risk factor(s), showing "rule of 30"

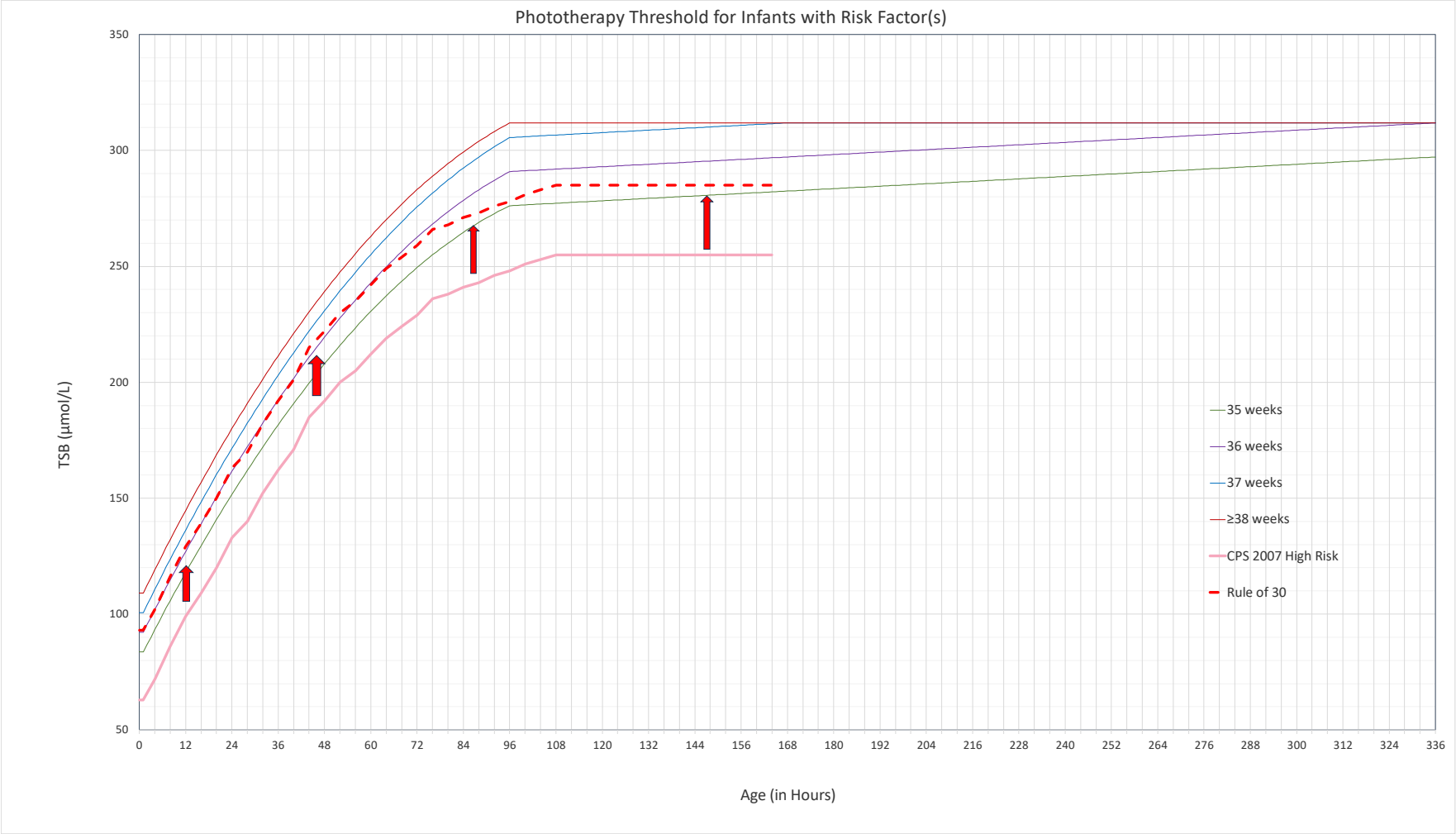


Figure S2a: Visual comparison 4: Exchange transfusion thresholds for infants with no risk factor

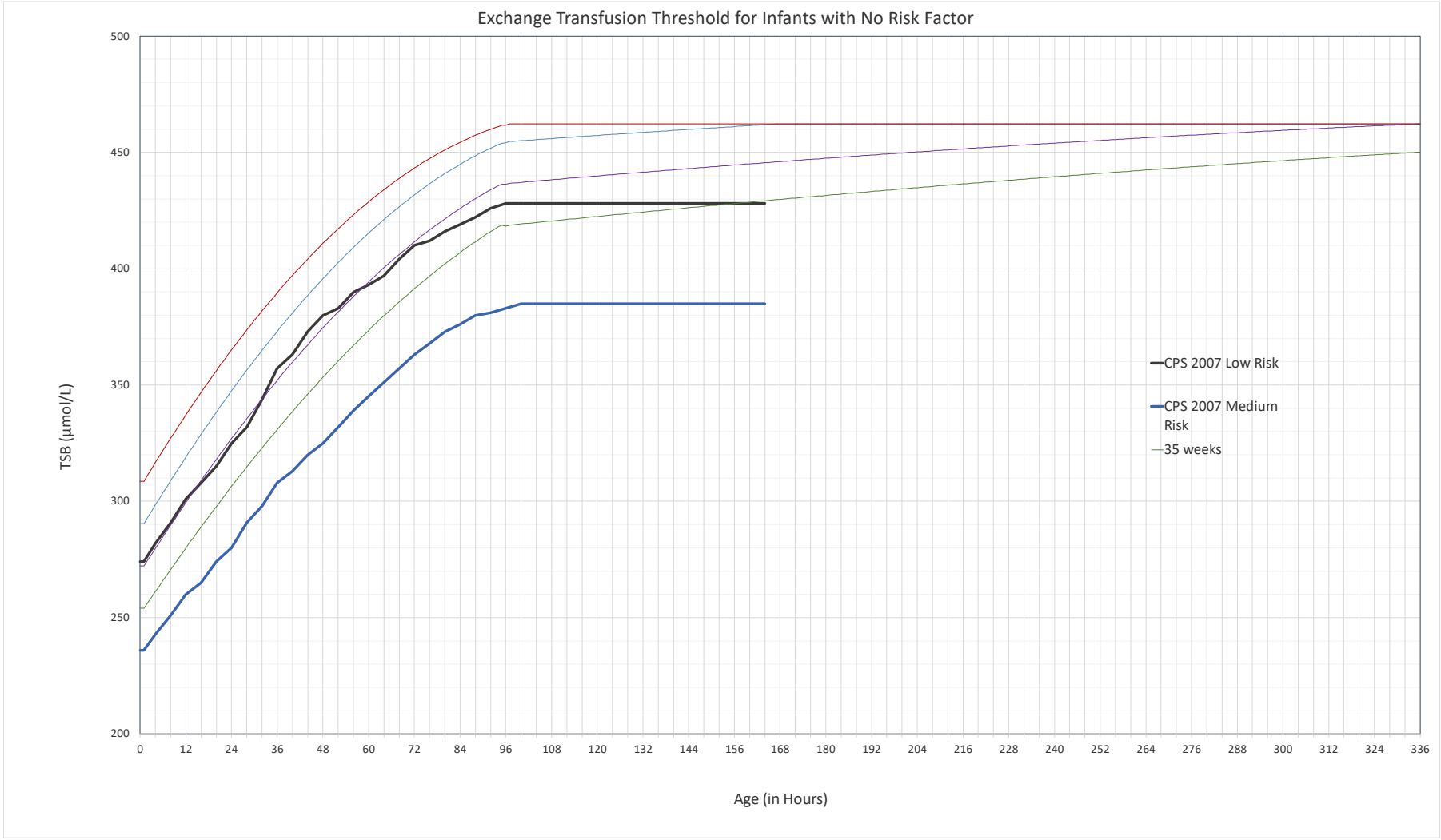


Figure S2b: Visual comparison 5: Exchange transfusion thresholds for infants with risk factor(s)

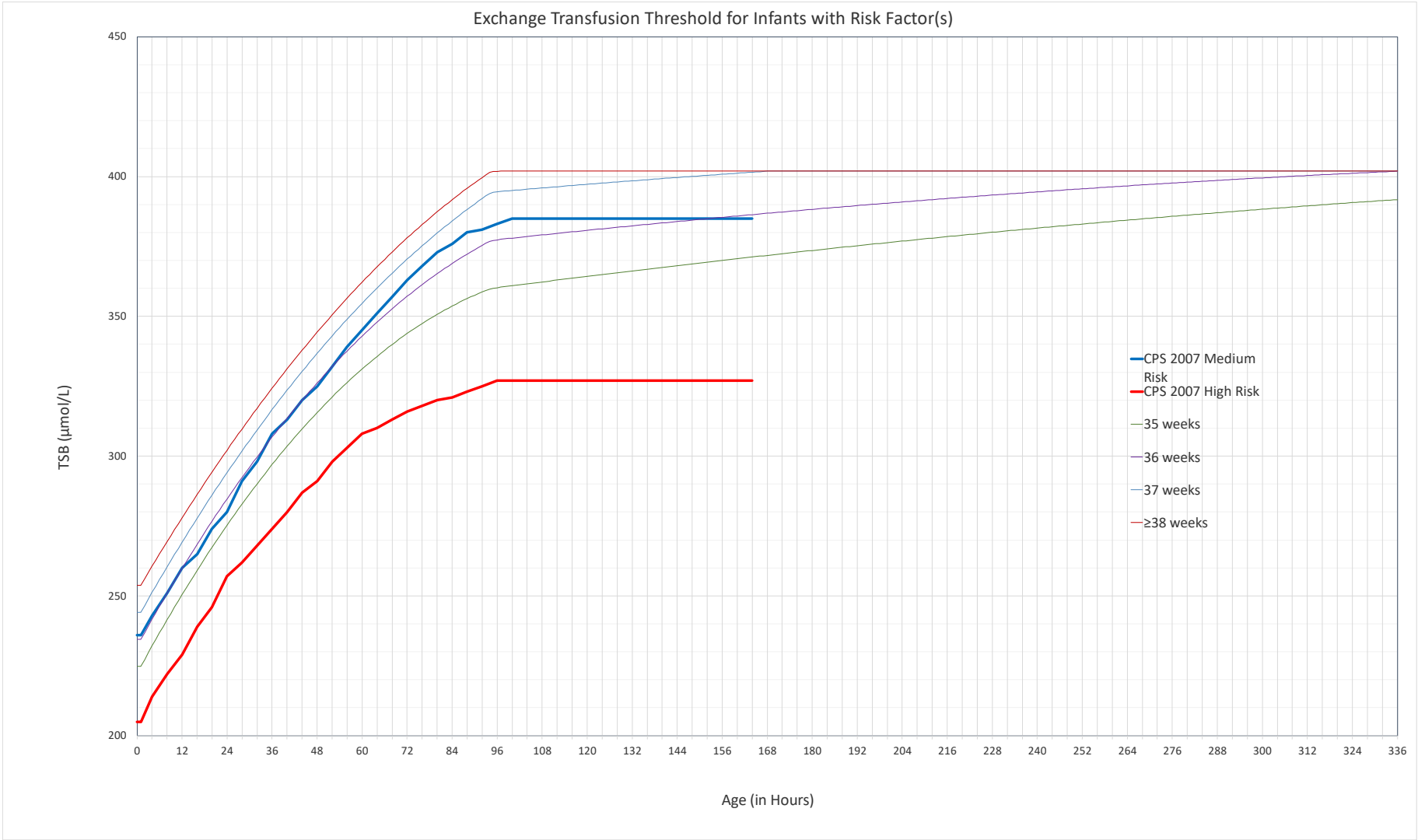
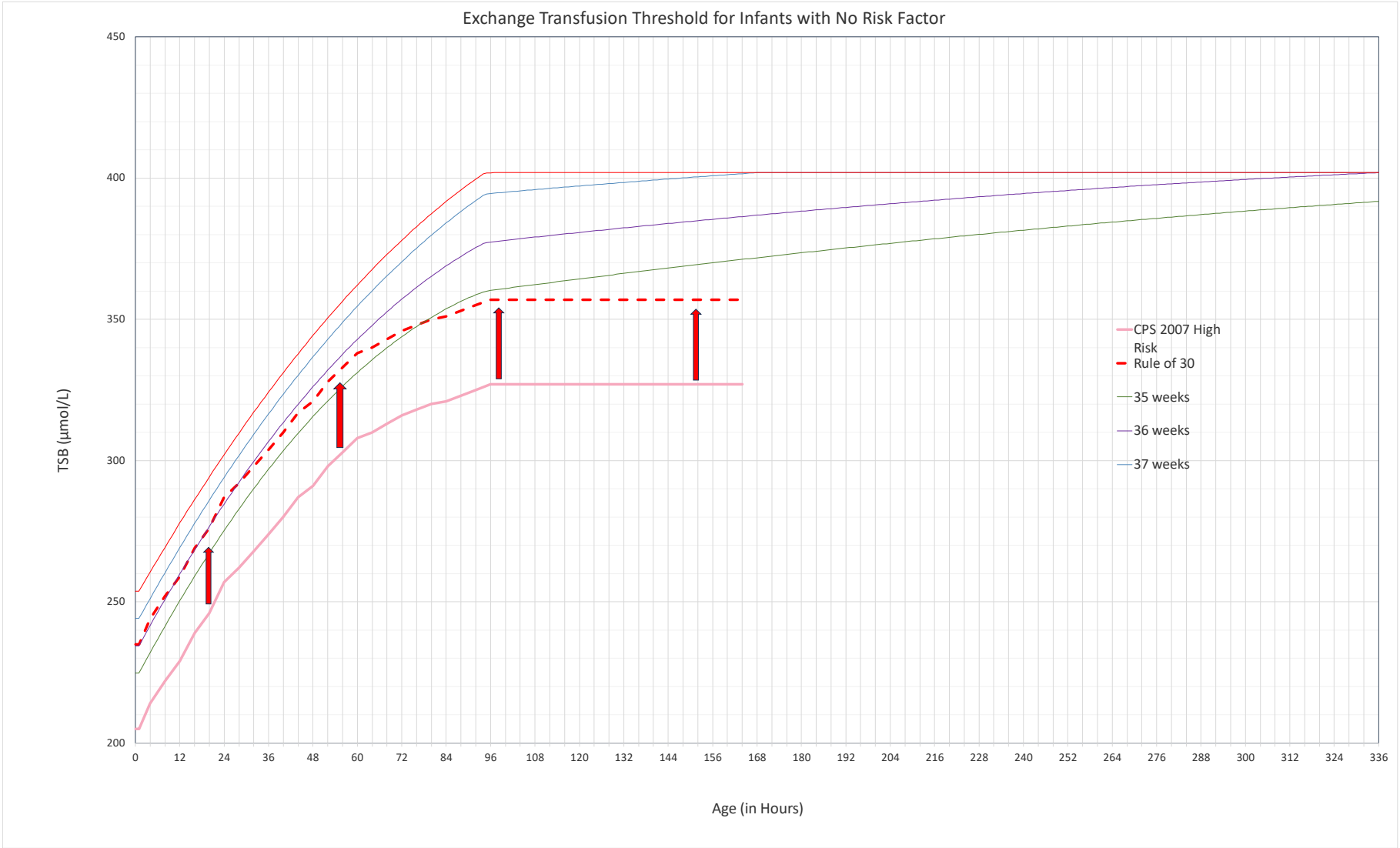


Figure S2c: Visual comparison 6: Exchange transfusion thresholds for infants with risk factor(s), showing the "rule of 30"



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