



TIPIT: A Randomised Controlled Trial of Thyroxine in Preterm Infants Under 28 weeks' Gestation

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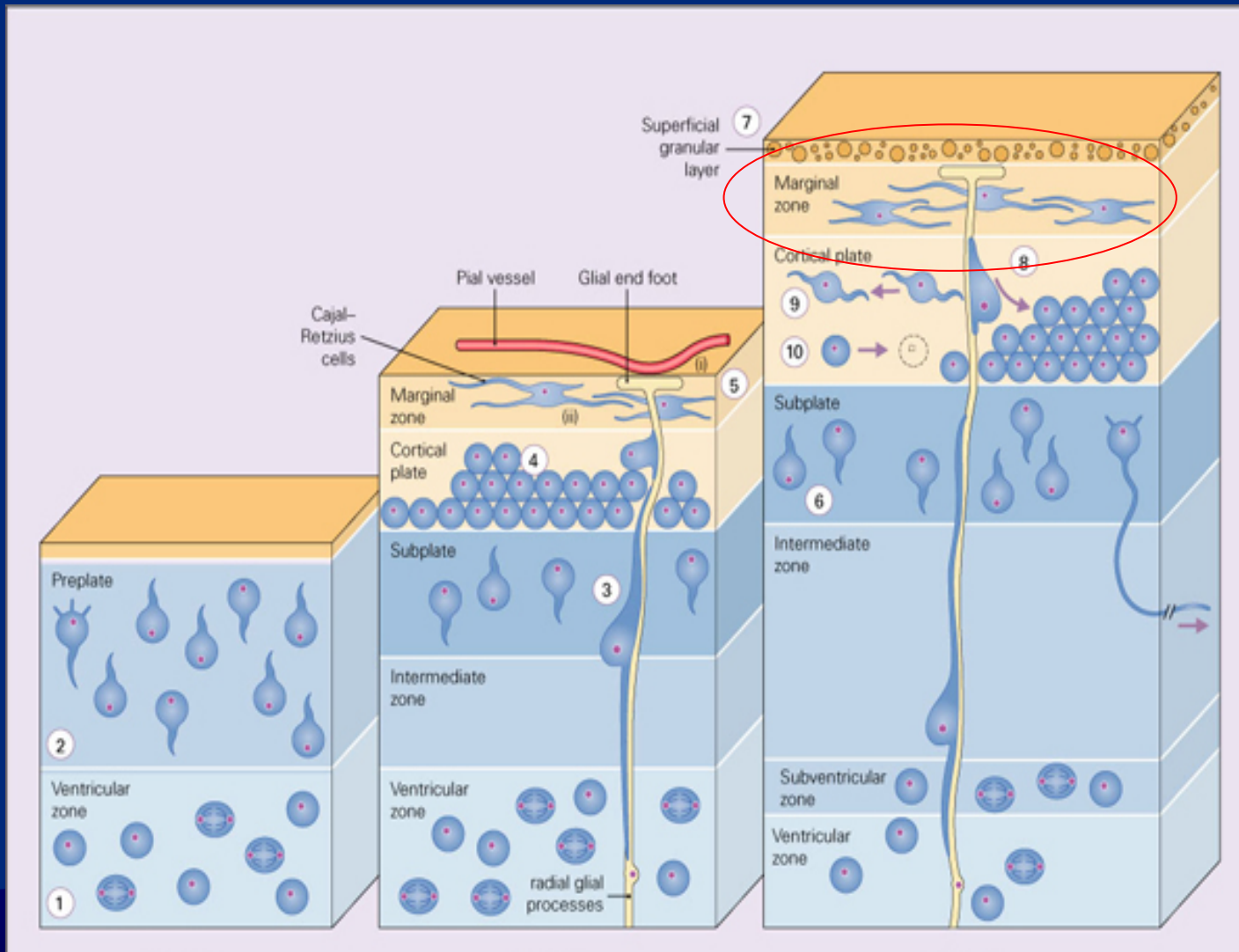
Introduction

- Scientific Background
- TIPIT study
- Regulatory framework and research networks

Background

- Infants born at extreme prematurity are at high risk of developmental disability
- Extreme prematurity represents a unique vulnerability in the developing brain

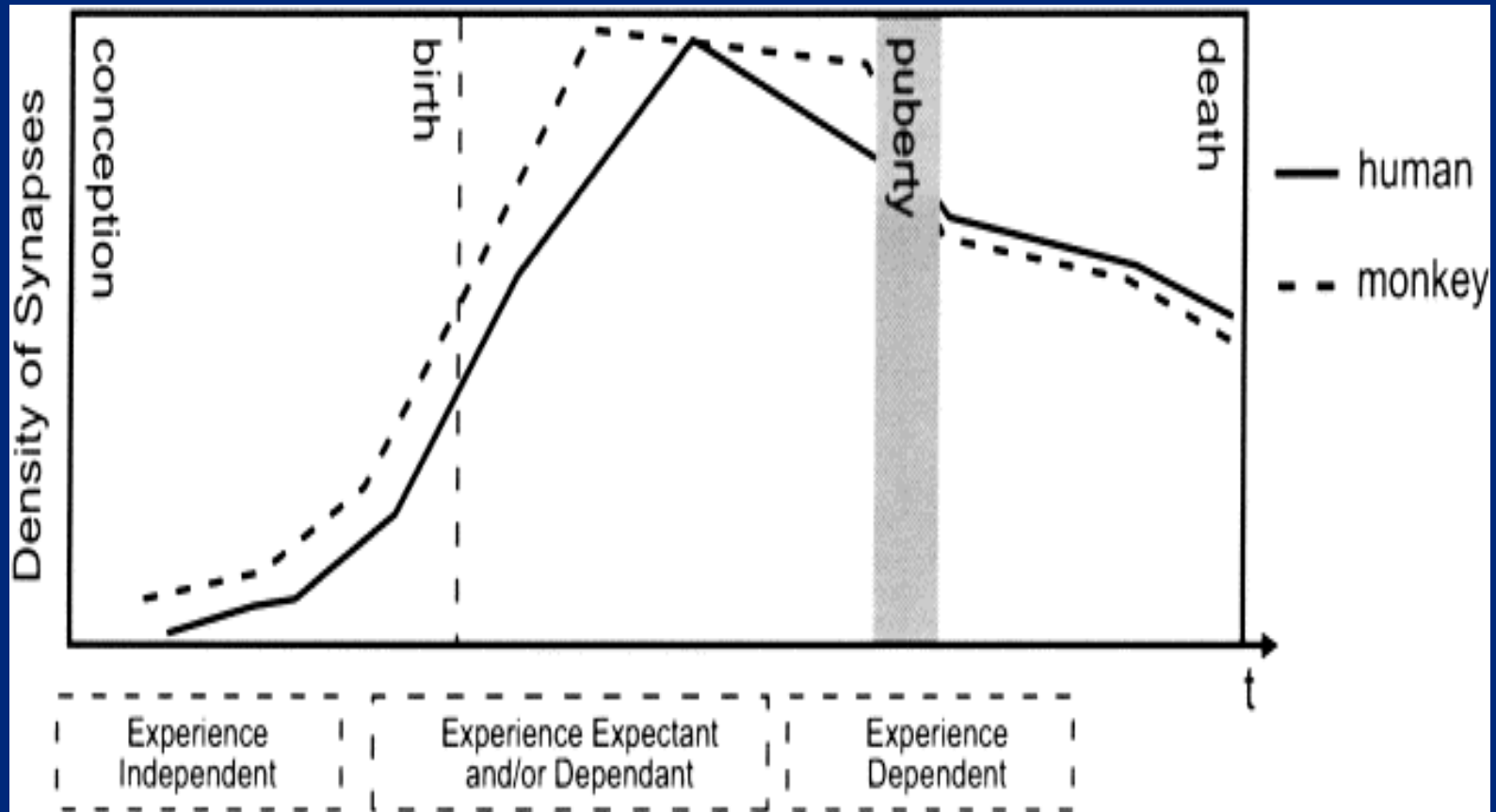
Neuronal Migration



10 w

30 w

Synaptogenesis in the mammalian cortex



Bourgeois JP , 1997

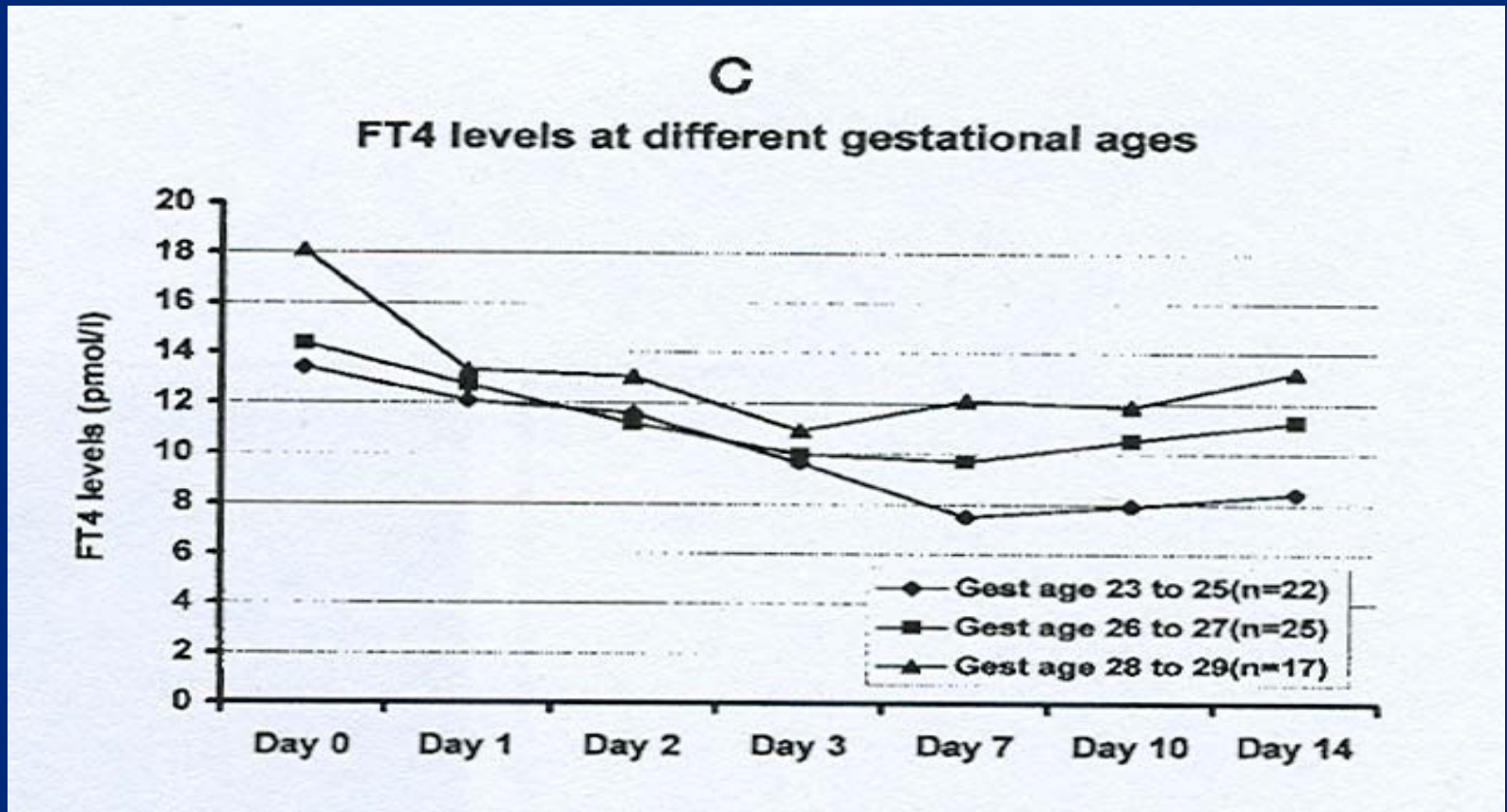
Thyroid hormones and the developing brain

- Thyroid hormones regulate synaptogenesis, neuronal integration, myelination and cell migration
- Maternal hypothyroxinaemia alters foetal cerebral cortex architecture

Hypothyroxinaemia in first weeks of life in preterm infants linked with poor neurodevelopmental outcome

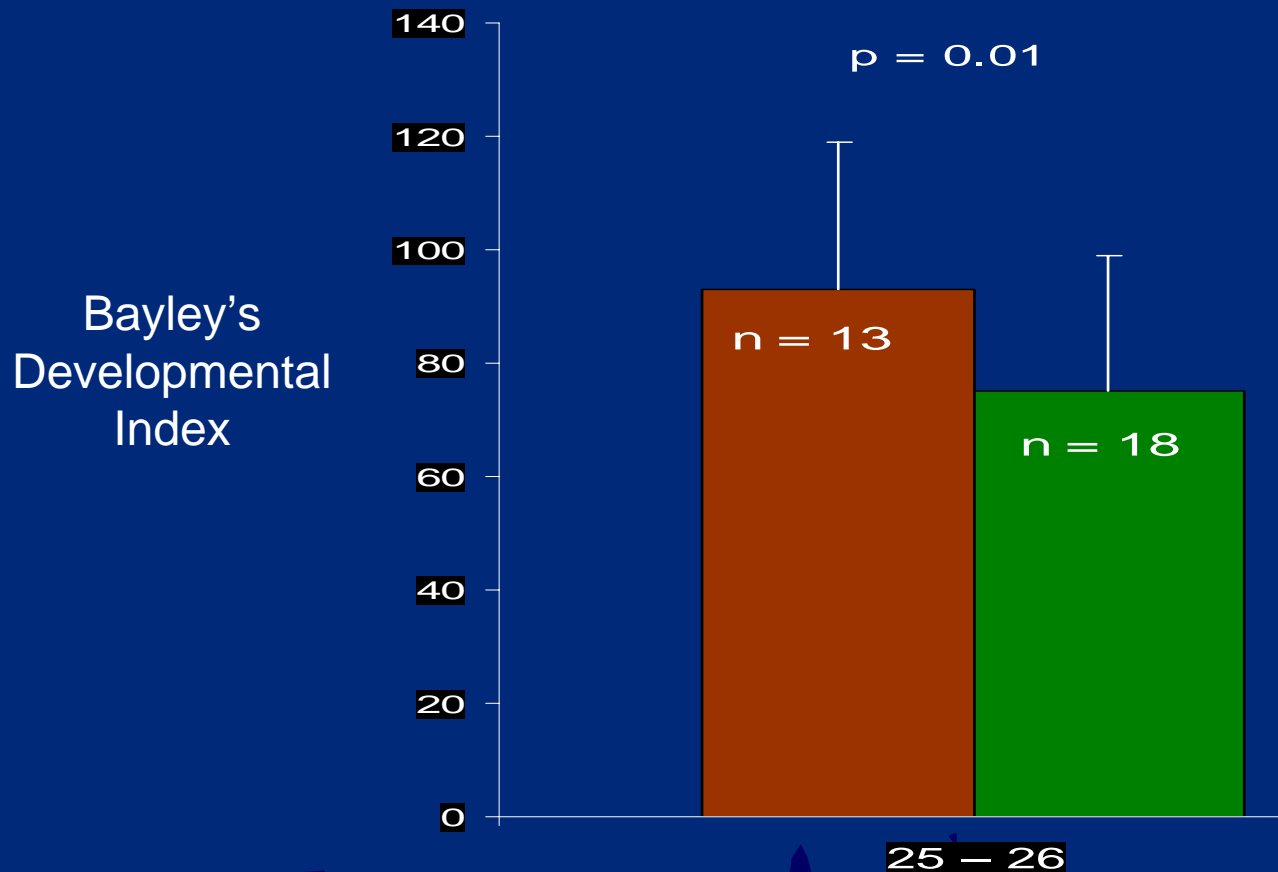
Study	Participants	Outcome associated with hypothyroxinaemia
Reuss NEJM 1996	463 preterm infants <33 weeks	4-fold increased risk of disabling CP at 2 years
Den Ouden Ped Res 1996	563 preterm <32 weeks	Higher incidence of neurological dysfunction at 5 and 9 years
Leviton A J Pediatr 1990	1414 preterm infants < 1500 g	Twice risk of cerebral white matter damage

Evidence of hypothyroxinaemia in preterm infants



Biswas 2002

Van Wassanaer 1997 NEJM- Subgroup Analysis



Rationale for TIPIT

No previous work in this patient group on

- relationship between thyroid status and brain development
- relationship between thyroid status and HPA axis
- effects of thyroxine levels on somatic growth
- relationship of thyroid status and size of thyroid gland
- circulating blood levels of thyroid hormones following the administration of thyroxine.



- **Objective**

To determine how thyroxine modulates brain development, HPA axis and somatic growth

- **Primary outcome**

Width of the sub-arachnoid space and head circumference at 36 weeks

Centres

- Recruiting centres (5)
 - Liverpool Women’s Hospital
 - St Mary’s Hospital
 - Hope Hospital
 - Arrowe Park Hospital
 - Royal Preston Hospital
- Non recruiting centres (23)
 - Cheshire and Merseyside
 - Greater Manchester Lancashire and South Cumbria



Regulatory Framework

- Guidelines from the UK Medicines for Human Use (Clinical Trials) Regulations, amended in 2006 by the EU Clinical Trials Directive
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- National Research Ethics Service (NRES)

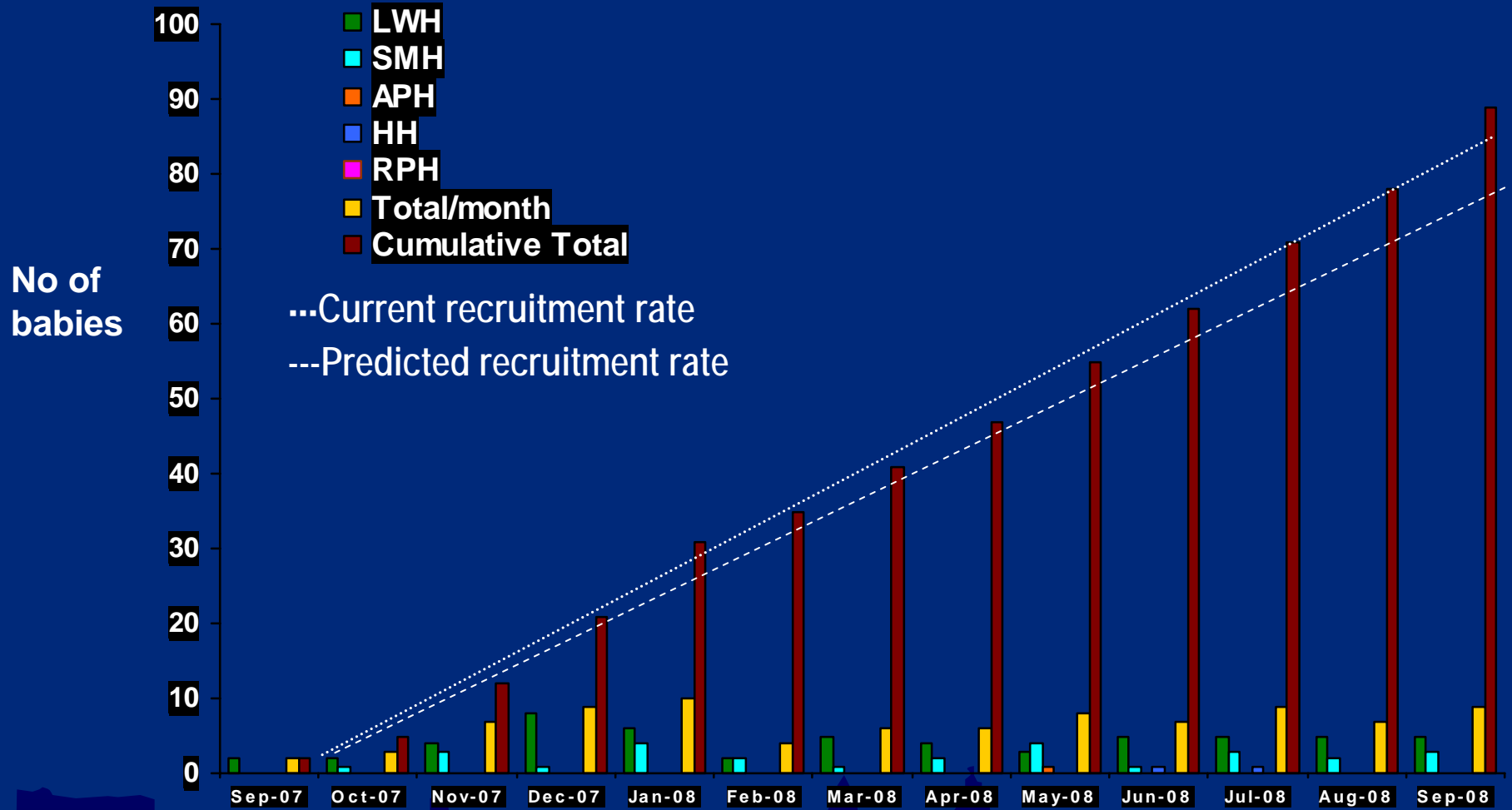
Research Governance

- Good Clinical Practice (GCP)
Ethical and scientific quality standard for the design, conduct and record of research involving humans
- Good Laboratory Practice (GLP)
Framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived
- Human Tissue Act (HTA)
Principles of lawful removal, storage and use of human tissue

The role of the Medicines for Children's Research Network

- site initiations
- gaining ethical and R&D approvals
- honorary contracts for investigators
- trial promotion
- monitoring of GCP compliance during the conduct of the trial

Total recruited : 89



TIPIT

- Trial promotion to 28 participating centres by MCRN
- Quarterly TIPIT newsletter
- Collaborators Meetings
- Presentation at the MCRN 2nd Annual Conference 2008
- Presentation at PRISM 2008
- BBC Radio 4 - 'Frontiers' programme 2008
- Ng SM, Turner M, Gamble C, M Didi, Victor S, Parkes L, Sluming V, Abernethy L, Weindling AM.

TIPIT: A Randomised Controlled Trial of Thyroxine in Preterm Infants under 28 weeks Gestation: Magnetic Resonance Imaging and Magnetic Resonance Angiography Protocol. *BMC Pediatrics* 2008, **8**:26

- Ng SM, Turner M, Gamble C, Didi M, Victor S, Weindling AM. TIPIT: A Randomised controlled trial of thyroxine in preterm infants born under 28 weeks gestation. *Trials* 2008, **9**: 17