

Priorities, choice of data, and practical issues for SafeBoosC-III follow up study



SafeBoosC III

SAFEGUARDING THE BRAIN OF OUR SMALLEST CHILDREN

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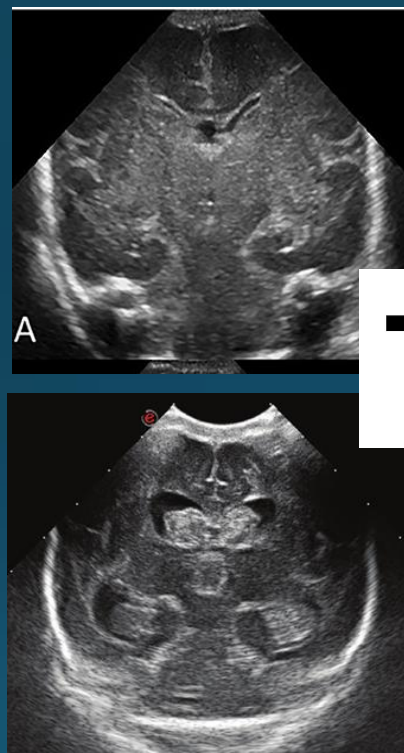
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Agenda

- Rationale behind the study
- Data collection
 - Clinical data
 - Parental questionnaire
- Prioritising for the co-primary outcomes
- Status – where are we now?
- Ancillary studies



Why is it necessary to perform the SafeBoosC-III follow up study?



36 weeks PMA endpoint →
clinically relevant

Two-year endpoint →
patient relevant



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Example from another field in neonatology

Cochrane review (Doyle et al, 2017):

Use of early systemic postnatal corticosteroids to prevent BPD in preterm infants

Short term outcomes → earlier extubation

→ decreased the risk of BPD until 36 weeks PMA

Long term outcomes → increased risk of adverse neurological outcome including cerebral palsy



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SafeBoosC-II 36 weeks PMA

- 166 extremely preterm infants randomised

Outcomes	NIRS (n=86)	Blinded NIRS (control) (n=80)	Relative change in % (95% CI)	Adjusted relative risk (95% CI)	Adjusted P value (unadjusted)
Primary					
Median (interquartile range) burden of hypoxia and hyperoxia (%hours)	36.1 (9.2-79.5)	81.3 (38.5-181.3) (n=78)	-58 (-35 to -74)	NA	<0.001*
Secondary					
All cause mortality at term	12/86 (14)	20/80 (25)	NA	0.50 (0.29 to 1.00)	0.10 (0.049)
Brain injury on cerebral ultrasonography:					
None	21/80 (26)	26/77 (34)	NA	—	0.11 (0.053)
Mild-moderate	49/80 (61)	33/77 (43)	NA	—	
Severe	10/80 (13)	18/77 (23)	NA	—	
Exploratory					
Median (interquartile range) burden of hypoxia (%hours)	16.6 (5.4-68.1)	53.6 (17.4-171.3) (n=78)	-58 (-24 to -76)	NA	0.0012*
Mean (SD) burden of hyperoxia (%hours)	1.2 (0.3-9.6)	1.1 (0.1-23.4) (n=78)	1 (-35 to 194)	NA	0.98*
Necrotising enterocolitis†	9/86 (11)	10/80 (13)	NA	0.83 (0.33 to 1.94)	0.69
Bronchopulmonary dysplasia‡	41/72 (57)	28/60 (47)	NA	1.27 (0.94 to 1.50)	0.20
Retinopathy of prematurity§	14/86 (16)	8/80 (10)	NA	1.64 (0.75 to 3.00)	0.20



SafeBoosC-II two year follow up

115/131 known to be alive infants
were followed up at 24 months of age

Table 3 Follow-up at two years of corrected age using Bayley-II, Bayley-III and ASQ

	Intervention	Control	p value
Bayley-II (n)	14	16	
Age at Bayley-II (months)	25.0 (1.4)	24.8 (1.1)	0.65
Mental Developmental Index	96.9 (13.9)	86.4 (13.8)	0.05
Psychomotor Developmental Index	83.9 (14.3)	87.4 (16.0)	0.54
Bayley-III (n)	30	23	
Age at Bayley-III (months)	24.3 (3.6)	25.2 (2.9)	0.34
Cognitive index	95.8 (19.9)	97.6 (10.2)	0.69
Language index	94.4 (18.8)	95.6 (13.4)	0.81
Motor index	91.8 (15.6)	99.1 (9.2)	0.07
Predicted Mental Developmental Index*	85.6 (21.1)	90.0 (15.4)	0.43
Combined outcome (n)	45	38	
Moderate neurodevelopmental impairment [§] (number)	8	3	0.21
Severe neurodevelopmental impairment ^{§§} (number)	2	3	>0.99



SafeBoosC-III two-year follow up

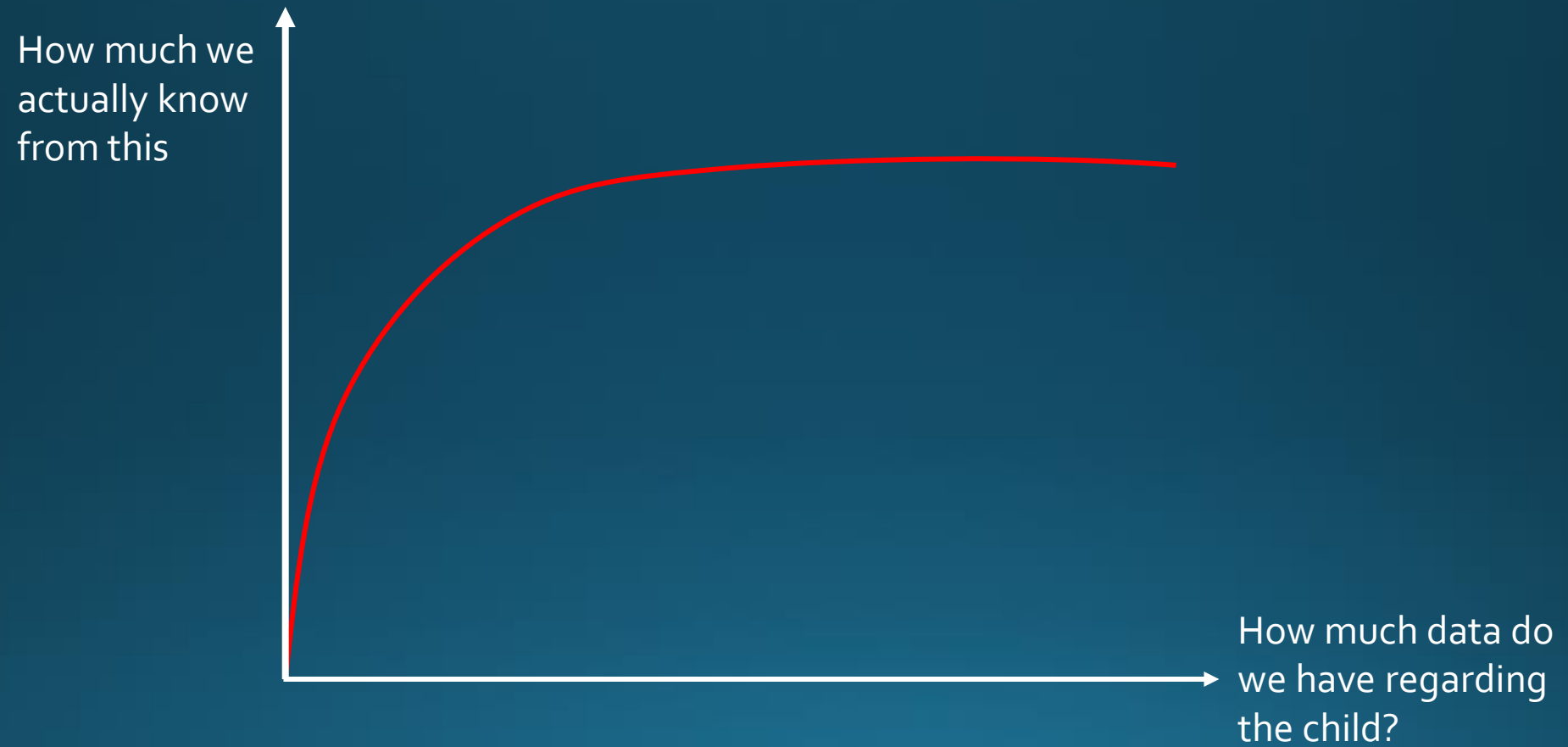
- 1260 infants alive at 36 weeks PMA
- Almost all centres will join
- From September 2021 – September 2024
- Assessment at two years of corrected age ($\pm$ six months)
 - Routine clinical data: Medical examinations + neurodevelopmental assessment and (or)
 - Parental questionnaire: PARCA-R + additional questions on general health and development

= different data approach than SFB-III



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Data approach



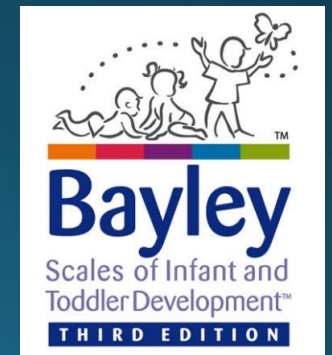
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Co-primary outcomes

- **Death or moderate-or-severe neurodevelopmental disability (binary)**
8% risk difference (n=730+730, alfa value of 2,5%, power of 80%)
- **Mean cognitive scores from Bayley-III assessment (continuous)**
5 points difference (n=300+300, alfa value of 2,5%, power of 80%)



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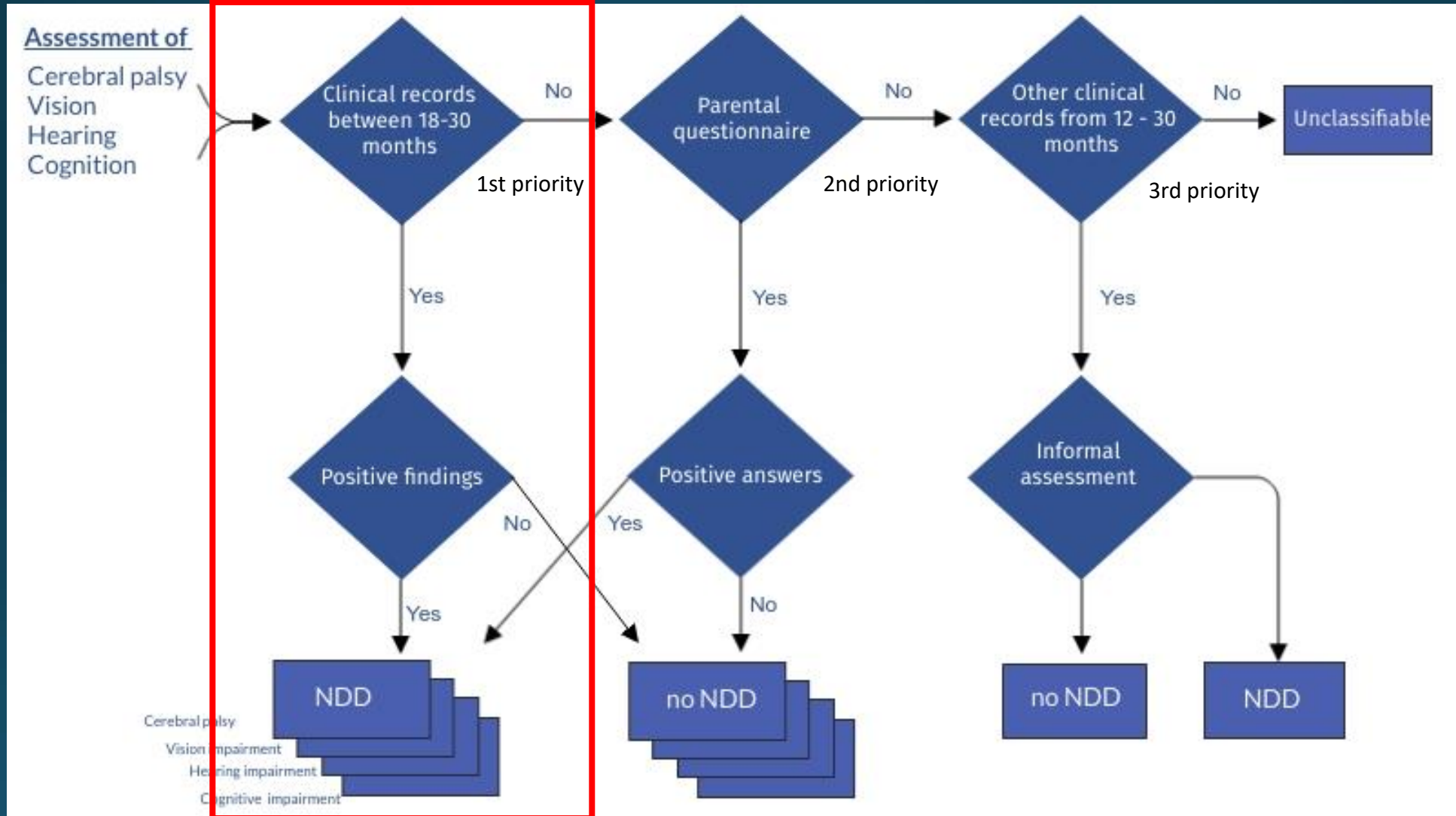


Moderate-or-severe neurodevelopmental disability (NDD)

Defined as

- **Cerebral palsy:** with functional impairment corresponding to GMFCS ≥ 2 or
- **Vision impairment:** defined as moderately reduced vision or worse or
- **Hearing impairment:** defined as hearing loss corrected with aids or worse
- **Cognition:** Standardised neurodevelopmental assessment score below -2 SD (or a positive informal assessment) or

Prioritisation of data for the co-primary outcome moderate-or-severe neurodevelopmental disability

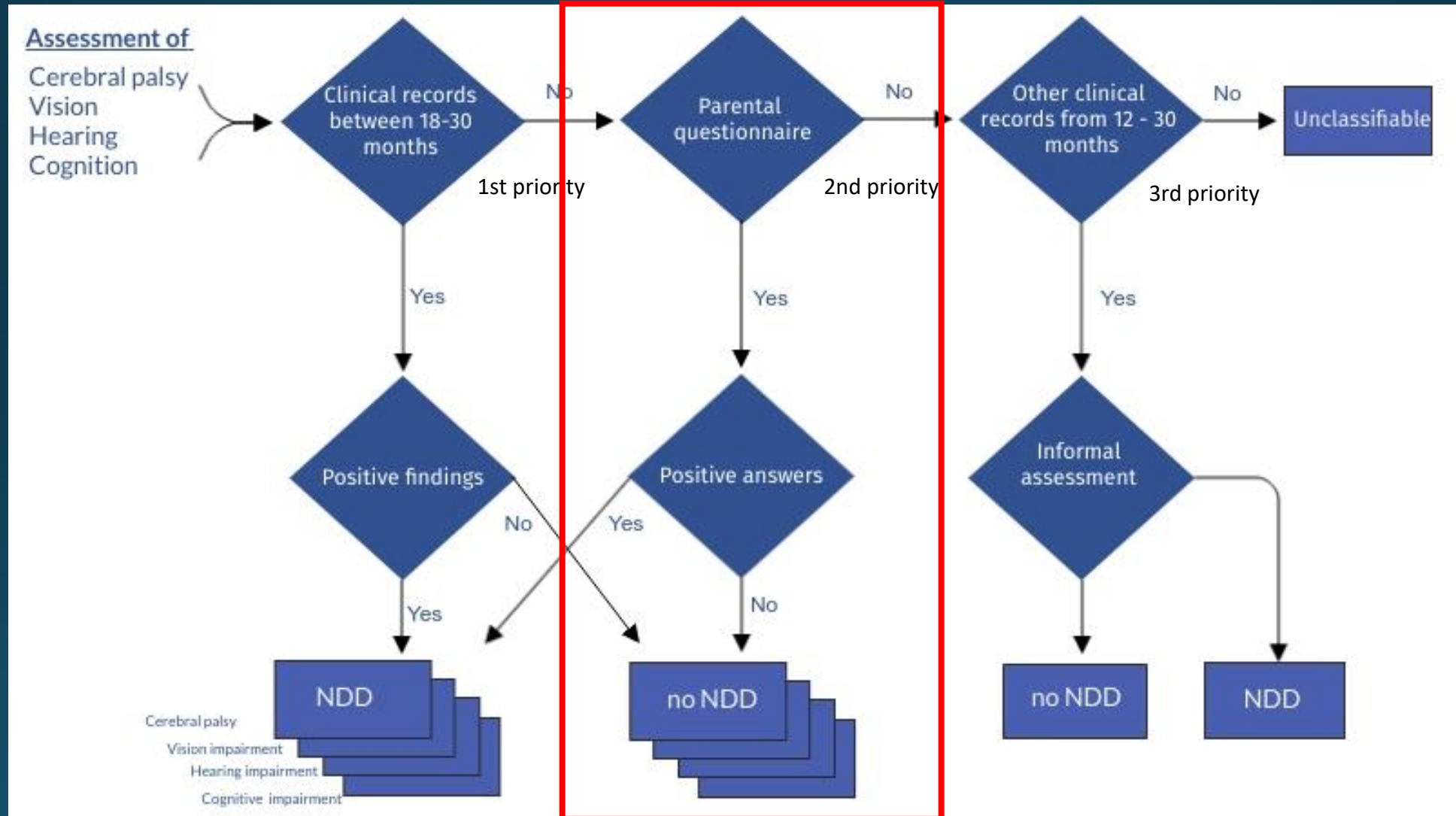


Blinded assessment of clinical data (18-30 months)

- Anthropometric measures
- Cerebral palsy diagnosis?
- Diagnosis of hearing impairment?
- Diagnosis of visual impairment?
- ROP treatment and/or diagnosis after 36 weeks of PMA?
- Chronic health problems?
- Daily medication?
- Neurodevelopmental assessment (preferably Bayley-III/IV)?
- Assessments done by psychologist/physician/physiotherapist etc



Prioritisation of data for the co-primary outcome moderate-or-severe neurodevelopmental disability



Parental questionnaire

- Section 1: PARCA-R non verbal cognitive scale (standardised neurodevelopmental assessment)
- Section 2: Health and development questionnaire
- Common denominator of our dataset
- Important to collect from all children



Parental questionnaire



<https://redcap.link/safeboosc>

A screenshot of the SafeBoosC III online questionnaire interface. At the top, there is a logo consisting of a blue brain with circuit-like patterns, followed by the text "SafeBoosC III" in blue and "SAFEGUARDING THE BRAIN OF OUR SMALLEST CHILDREN" in smaller black text. Below this, the title "The SafeBoosC-III two year follow up study" is displayed. A "Page 1 of 1" indicator is on the right. The main content area has a light green background and contains a language selection prompt in multiple languages: "Please select language", "Vælg venligst sprog", "Por favor seleccione idioma", "Bitte Sprache auswählen", "Si prega di selezionare la lingua", "Veuillez sélectionner la langue", "Lütfen dil seçin", "Velg språk", "Proszę wybrać język", "Vyberte prosím jazyk", "Επιλέξτε γλώσσα", and "请选择语言". To the right of the text is a dropdown menu with a list of languages: English, Dansk (Danish), Español (Spanish), Deutsch (German), Italiano (Italian), Français (French), Türk (Turkish), Norsk (Norwegian), Polskie (Polish), Český (Czech), Ελληνικά (Greek), and 中文 (普通话) (Chinese, mandarin). A "Submit" button is located at the bottom right of the language selection area. A "Resize font" icon is in the top right corner.

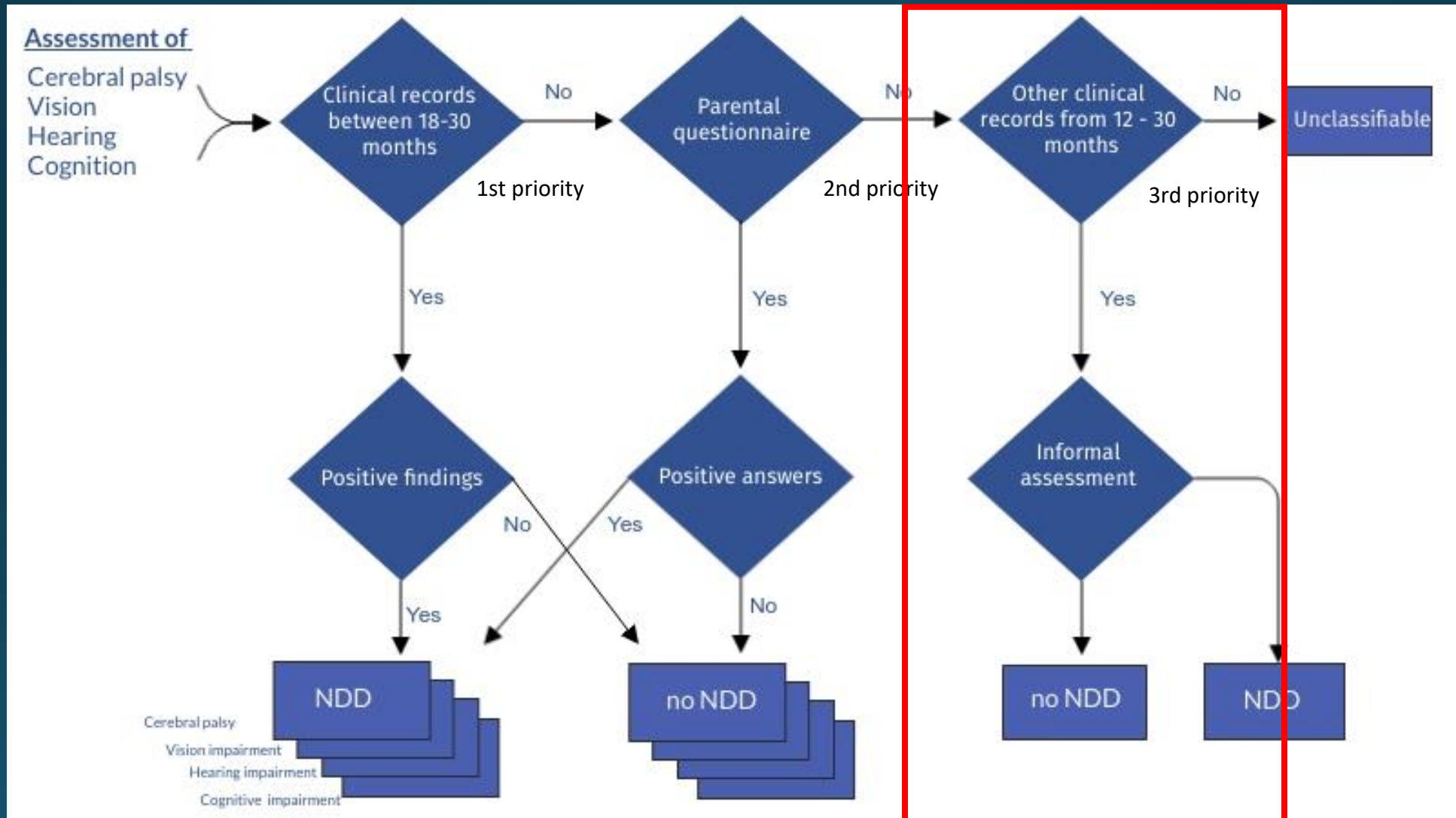
Online platform:
Send link to parents with study ID
(DK01001, IT07003, TR02047 etc)



Paper version:
Have parents fill out in clinic
and put in answers manually
through online platform



Prioritisation of data for the co-primary outcome moderate-or-severe neurodevelopmental disability



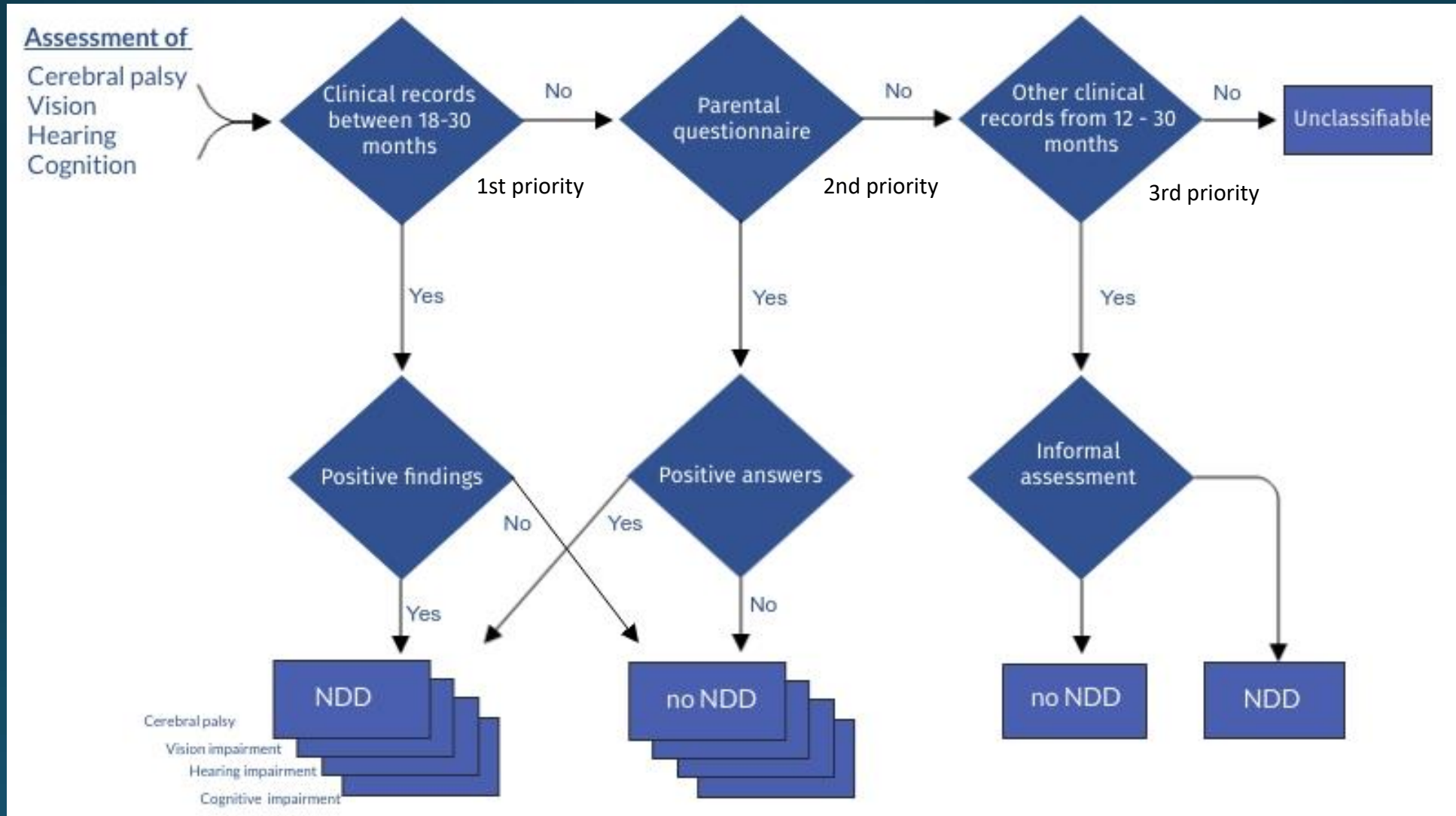
Informal assessment

- When there are no relevant health care records between 18-30 months
- When there has not been conducted any standardised neurodevelopmental assessments (Bayley-III, PARCA-R, other)

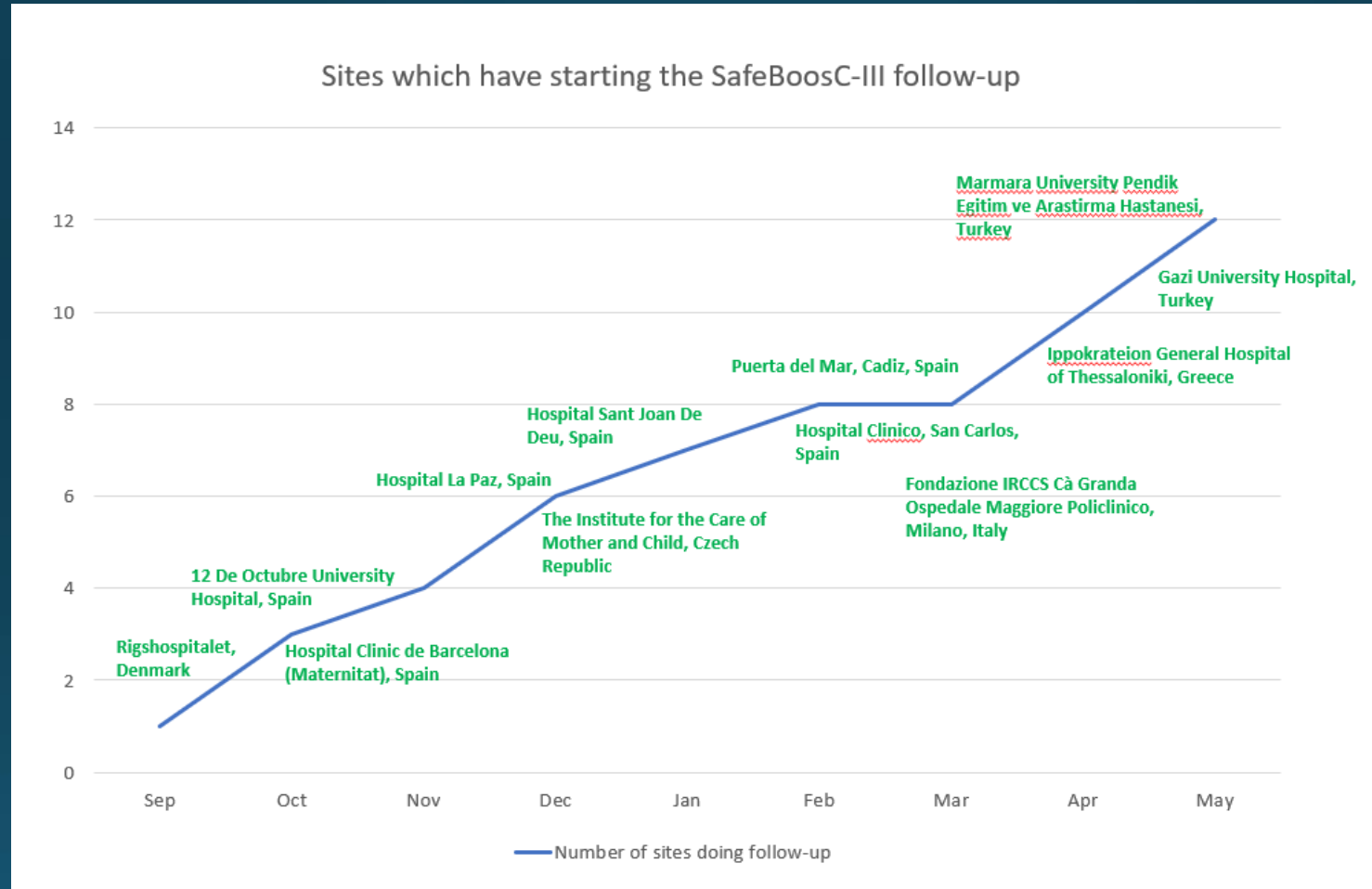
→ Informal assessment: all health care records from corrected age 12 months will be informally assessed to conclude whether or not the child has moderate-or-severe neurodevelopmental disability



Prioritisation of data for the co-primary outcome moderate-or-severe neurodevelopmental disability



Status – where are we now?

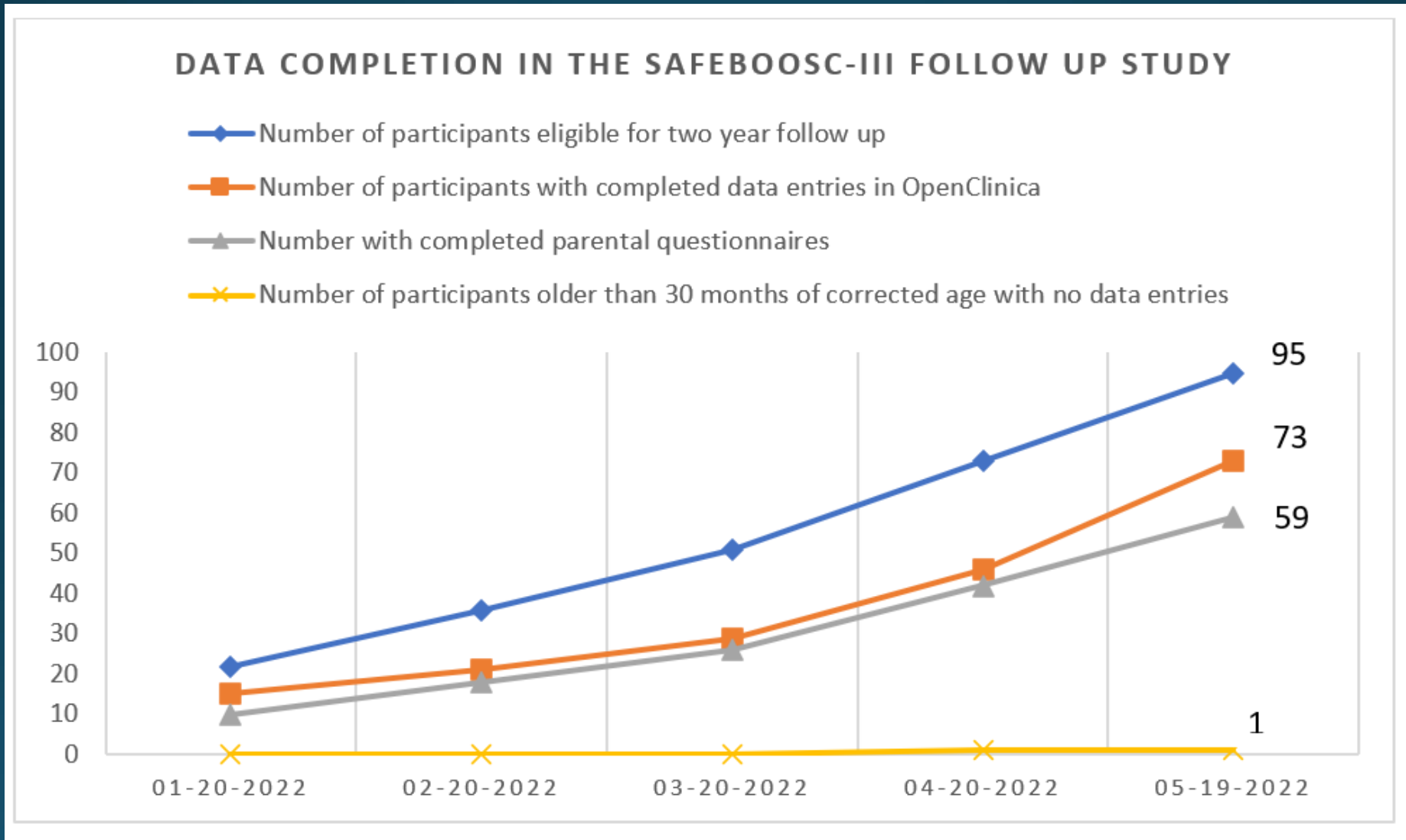


30 more centres will start follow up in 2022



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Status – where are we now?



Ancillary study: CogniTOT (Deirdre Murray)



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**Touchscreen applications
clinically proven to detect
learning delay in young
children**

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Ancillary study: CogniTOT

- Bayley assessments → heavily reliant on language skills
- Language free assessment tool → measures the overall cognitive ability of the child
- Internal consistency and good concurrent validity with Bayley III



Questions?



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