Methodological challenges in a large cluster RCT using routine data sources and suggested solutions: lessons learned from the GBS-3 trial

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Background

- Common methodological challenges in the design and analysis of cluster randomised controlled trials (cRCTs) are well documented.
- If not properly considered may introduce biases: identification, recruitment, baseline imbalance, loss of clusters, and incorrect design and analysis.
- Other challenges exist but are not well documented.
- This presentation highlights some of the unanticipated challenges which we have encountered in implementing the GBS3 trial and how we have dealt with them.

Main challenge

- Longer waiting times for intervention implementation due to logistical challenges and the effect of COVID-19
- As a result, data collection from risk-factor sites would have started at an earlier time frame than the intervention sites (Fig 1)

Days from randomisation to start of data collection for 22 sites that have been given green light to open, mean (SD)		
Risk factor* (n=9)	**Routine testing (n=13)**	
151 (38)	311 (89)	
	ECM (n=6)	**Rapid test (n=7)**
	248 (60)	365 (75)

*At trial planning stage, we assumed the intervention sites would open to data collection 4 months after randomisation (including 12 week implementation)

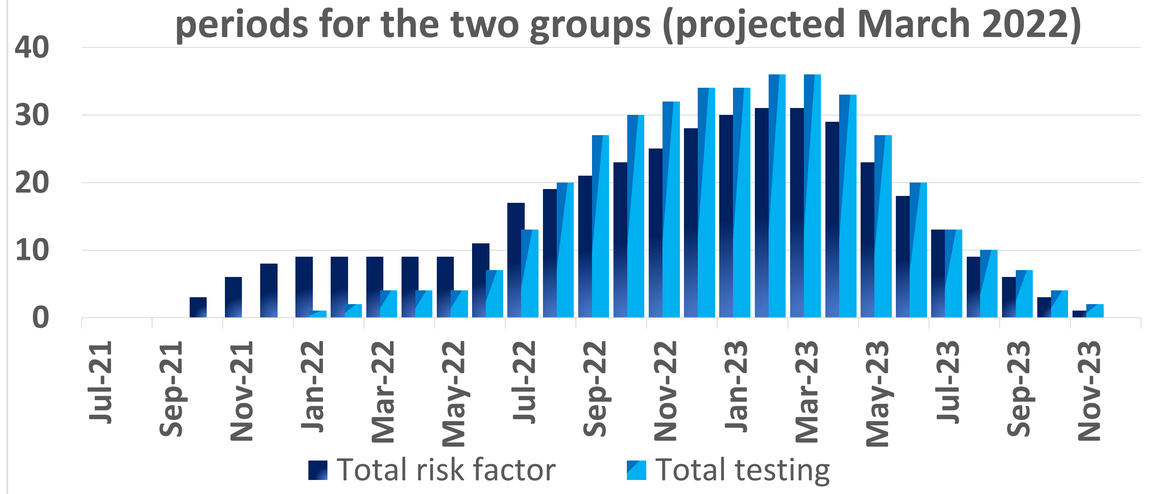
Proposed solution

- Extend the data collection period for risk-factor sites that were already open and delay the opening of sites that were randomised to risk-factor until more intervention sites were ready for opening.
- Going forward, sites randomised at the same time to be opened to data collection at the same time.
- This was to ensure data used for the comparison of the two strategies is contemporaneous.

The GBS3 Trial

- An ongoing cRCT assessing whether routine testing of women for Group B Streptococcus colonisation (using Enriched Culture Medium (ECM) or rapid test) either in late pregnancy or during labour reduces the occurrence of early-onset neonatal sepsis, compared to the current risk factor-based strategy.
- Outcomes obtained from routinely collected health data (RCHD).
- Up to 80 sites (obstetric units): ~320,000 women
- Status so far: 43 randomised, 26 have had site initiation visits and 22 have been given green light to open.

Fig 1. Potential distortion between data collection periods for the two groups (projected March 2022)



Other challenges encountered

- Potential post-randomisation changes to cluster composition due to merging of NHS trusts.
- Potential dilution of the treatment effect in the ITT analysis (intended place of birth) occasioned by change of intended location of childbirth for women who had been offered the ECM.
- Not being able to recruit the target number of sites.

Discussion

- Despite adequate planning we still faced a number of unanticipated challenges.
- Our proposed solutions were possible due to the use of RCHD, but careful consideration need to be taken when directly collecting individual patient-level data.

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