The use of Electronic Health Records in the design of trials of complex surgical interventions: identifying the contribution of multiple providers

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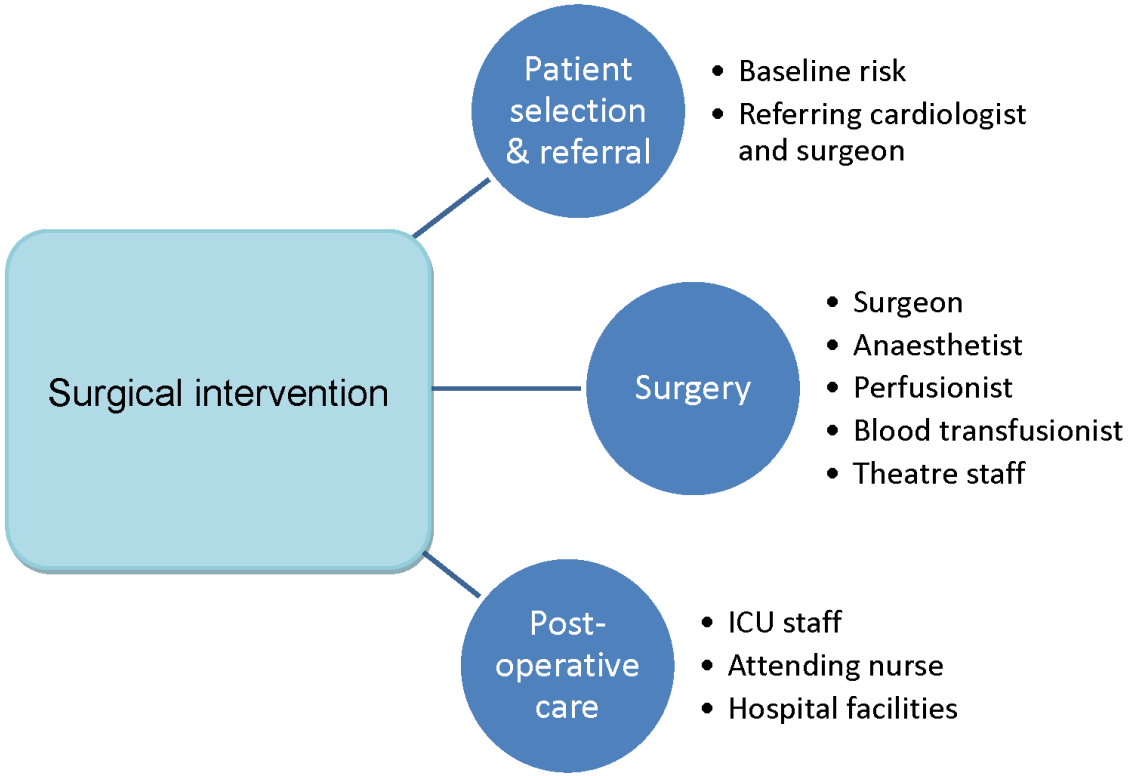
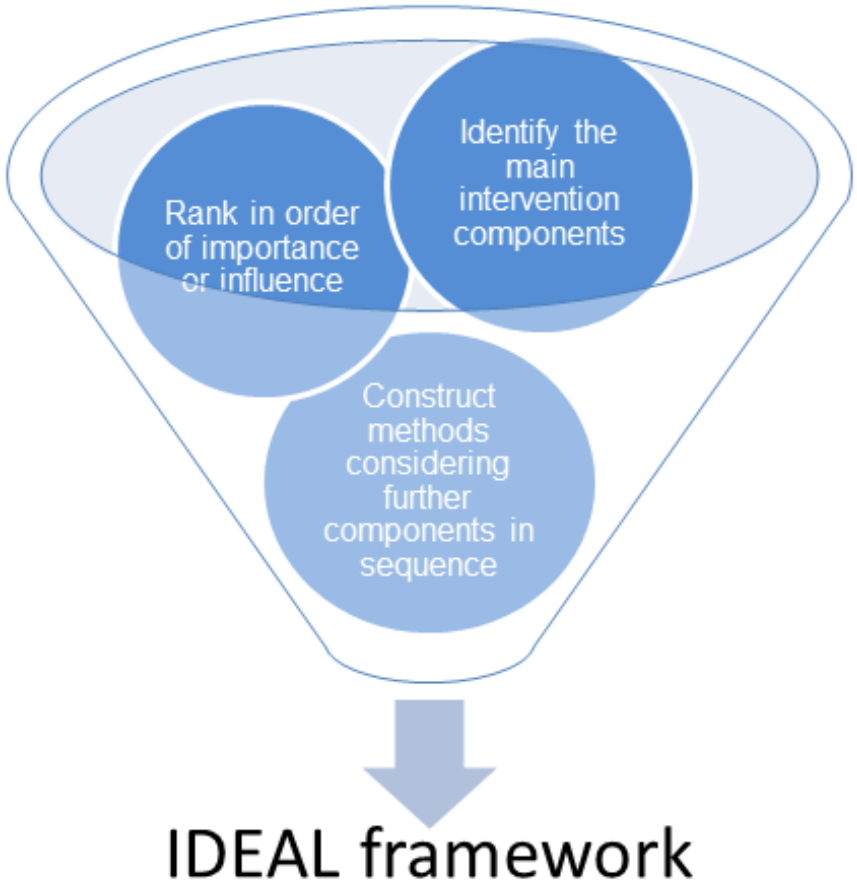
Background

* **Complex Interventions**: composed of several interacting components acting independently as well as interdependently.



Background

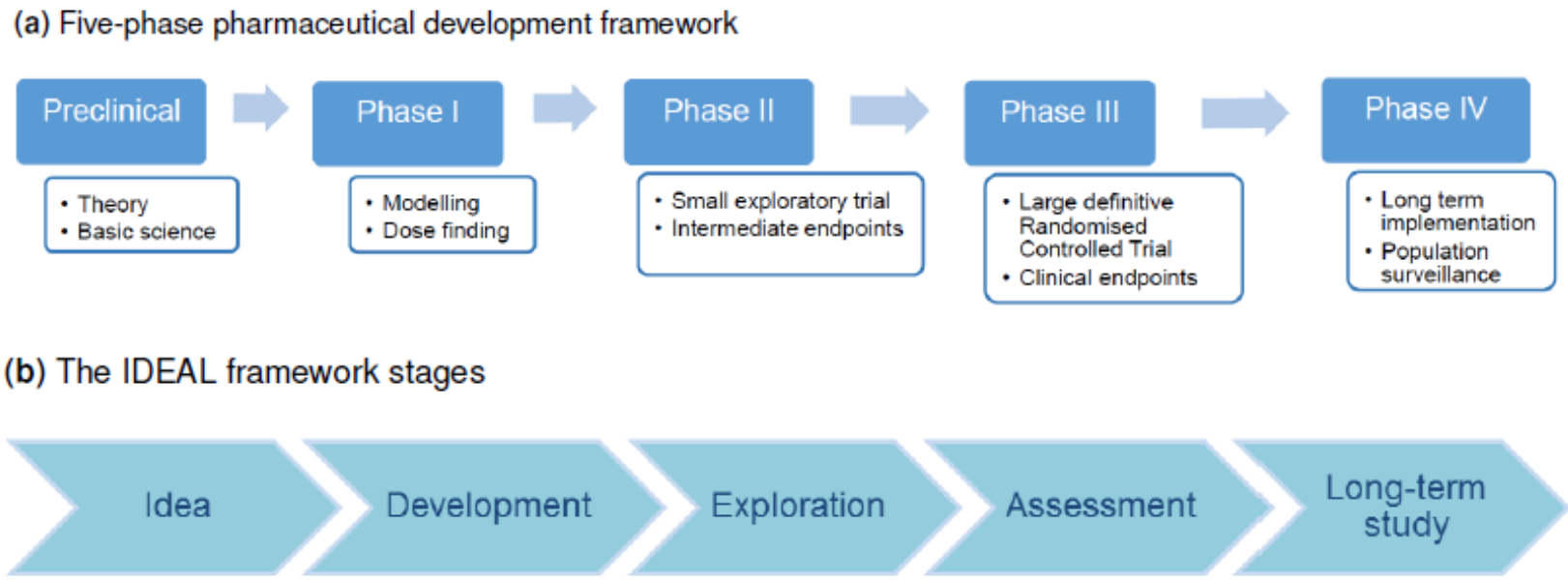
* **Building up** complex surgical evaluations:



↪ Five-stage paradigm delineating the development of innovative surgical procedures.

Background

* *IDEAL stages*

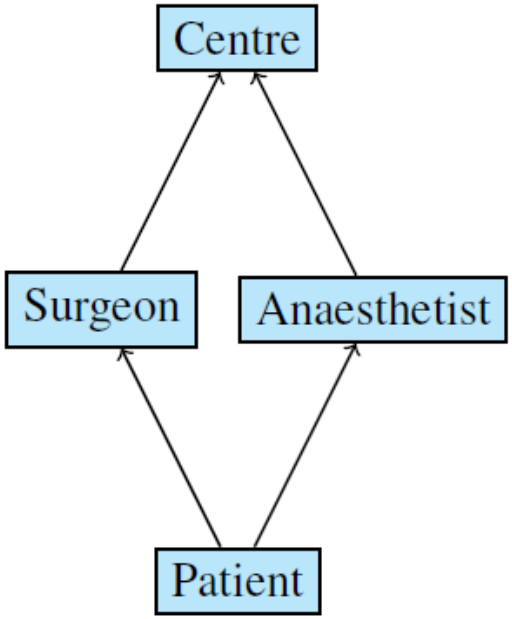


↪ Highlights study designs and reporting standards most useful at each stage of this more complex setting.

Aims

- ↪ Examine the extent to which patients treated by the *same medical team* are more likely to have the same outcome.
- ↪ Establish the individual surgeon and anaesthetist effects on outcome.
- ↪ Establish the effect of the Centre and the implications of multiple clustering sources for trial design.

Random effects models



↪ Explicitly account for grouped data structure i.e. patients grouped within anaesthetists and surgeons, grouped within Centres.

Random effects models

- clusters treated as a random sample from a general population $\Rightarrow$ results generalisable to the whole population.
- Improved accuracy in the standard errors and p-values of the regression coefficients.
- separate estimation of operator effects and operator associated covariates.
- *Intra-Class Correlation coefficient* (ICC) $\longrightarrow$ Proportion of variation in outcome attributed to:
  - Centre
  - Surgeons
  - Anaesthetists
  - Patients

Random effects models

Models:

1. Surgeon random effects - two-level random intercept model.
2. Anaesthetist random effects - two-level random intercept model.

Random effects models

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1. Surgeon random effects - two-level random intercept model.
2. Anaesthetist random effects - two-level random intercept model.

↪ Cannot be extended to 3-level hierarchical models as data structure not fully nested.

3. *Cross-Classified model* accounting for lower level units belonging to more than one clusters which are not nested.

Application

- Large case series study (>110000 patients) in 10 of 36 specialist cardiac UK Centres during 10 years (2002-2012).
- 110769 operations conducted by 127 surgeons and 190 anaesthetists.
- Binary response variable: in-hospital death up to 3 months post-operatively.
- First level covariate: the logistic-EuroSCORE of each patient.

Application

Three-level random intercept model

$$logit(\pi_{ijk}) = \beta_{0ij} + \sum_{w} \beta_w (x_{ijkw} - \overline{x_w}) \quad (1)$$

where $y_{ijk}|\pi_{ijk} \sim Binomial(1, \pi_{ijk})$.

π_{ijk} the probability of an in hospital death for the k^{th} patient treated by the j^{th} surgeon and i^{th} Centre.

$e_{ijk} \sim Logistic(0, 1) \Rightarrow \sigma_e^2 = \pi^2/3$

x_{ijkw} the w^{th} covariate for the k^{th} patient treated by the j^{th} surgeon and i^{th} Centre.

Three-level random intercept model

$$logit(\pi_{ijk}) = \beta_{0ij} + \sum_{w} \beta_w (x_{ijkw} - \overline{x_w}) \qquad (2)$$

$\beta_{0ij} = \alpha + u_{ij} + z_i$, $z_i \sim N(0, \sigma_z^2)$ the i^{th} Centre random intercept.

$u_{ij} \sim N(0, \sigma_u^2)$ for the j^{th} surgeon in the i^{th} Centre.

Application

Three-level cross-classified model

$$logit(\pi_{ijkl}) = \beta_{0ijk} + \sum_{w} \beta_w (x_{ijklw} - \overline{x_w}) \quad (3)$$

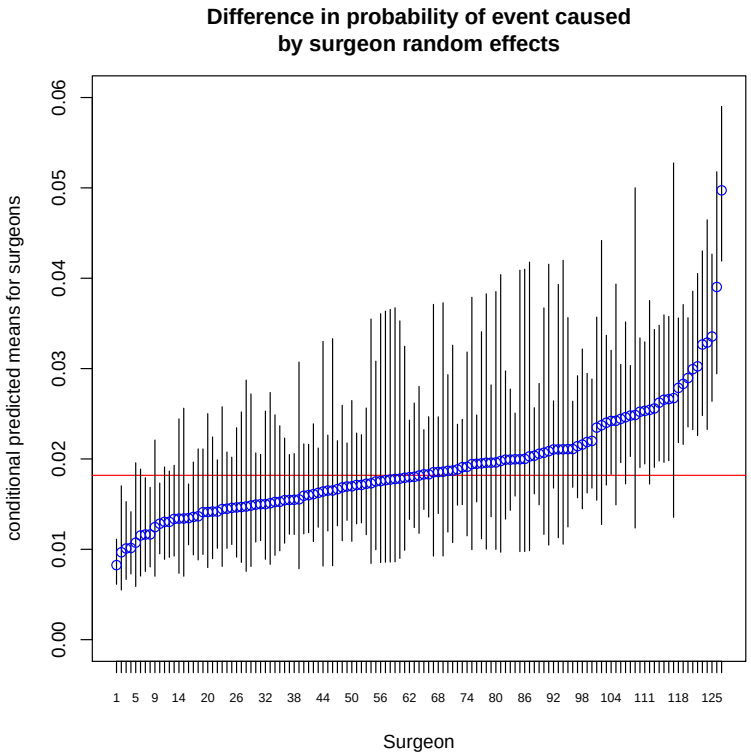
$\beta_{0ijk} = \alpha + u_{ij} + v_{ik} + z_i$, $z_i \sim N(0, \sigma_z^2)$ the i^{th} Centre random intercept.

$u_{ij} \sim N(0, \sigma_u^2)$ for j^{th} surgeon in i^{th} Centre.

$v_{ik} \sim N(0, \sigma_v^2)$ for the k^{th} anaesthetist.

Results

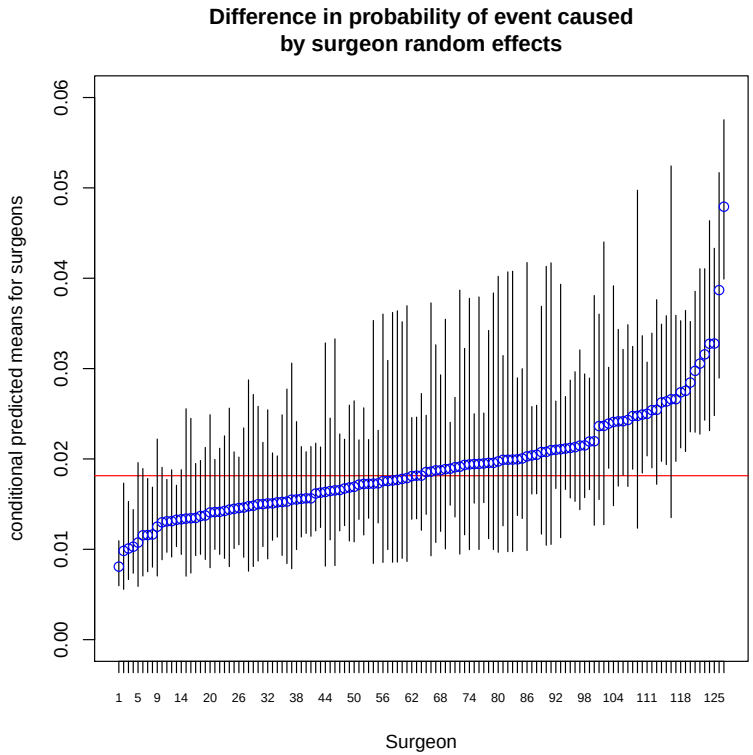
Three-level model



(a) Surgeon "forest plot" adjusted for case-mix and Centre

ICC_S=4.06%

Three-level cross-classified model

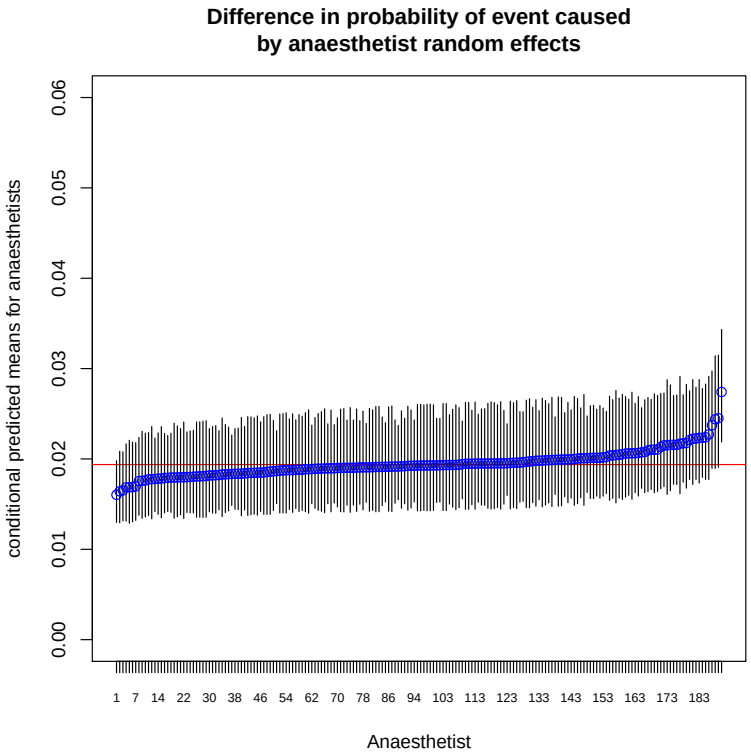


(b) Surgeon "forest plot" adjusted for case-mix and both for Anaesthetist and Centre

$ICC_{S/A}$=4.01%

Results

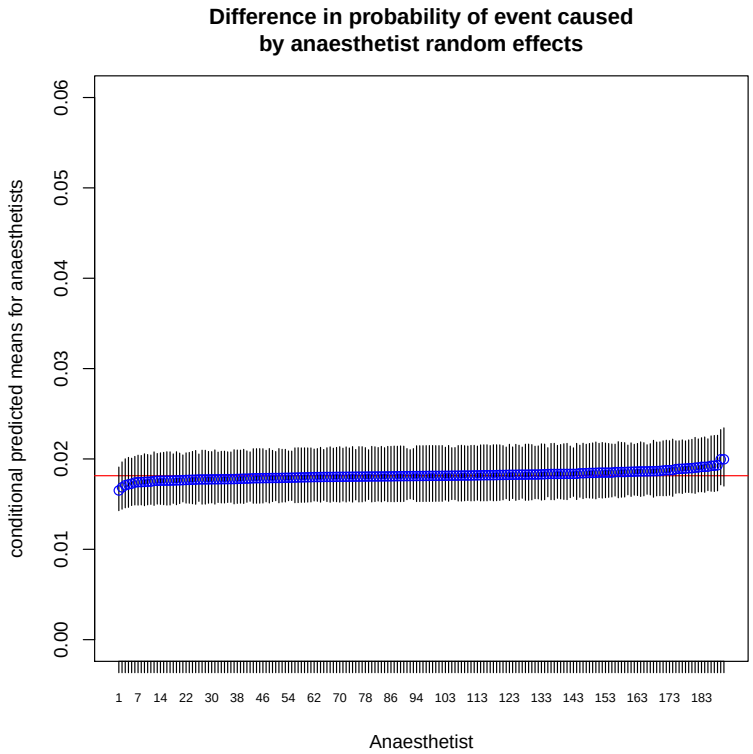
Three-level model



(c) Anaesthetist "forest plot" adjusted for case-mix and Centre

ICC_A=0.72%

Three-level cross-classified model



(d) Anaesthetist "forest plot" adjusted for case-mix and both for Surgeon and Centre

$ICC_{A/S}$=0.24%

Results

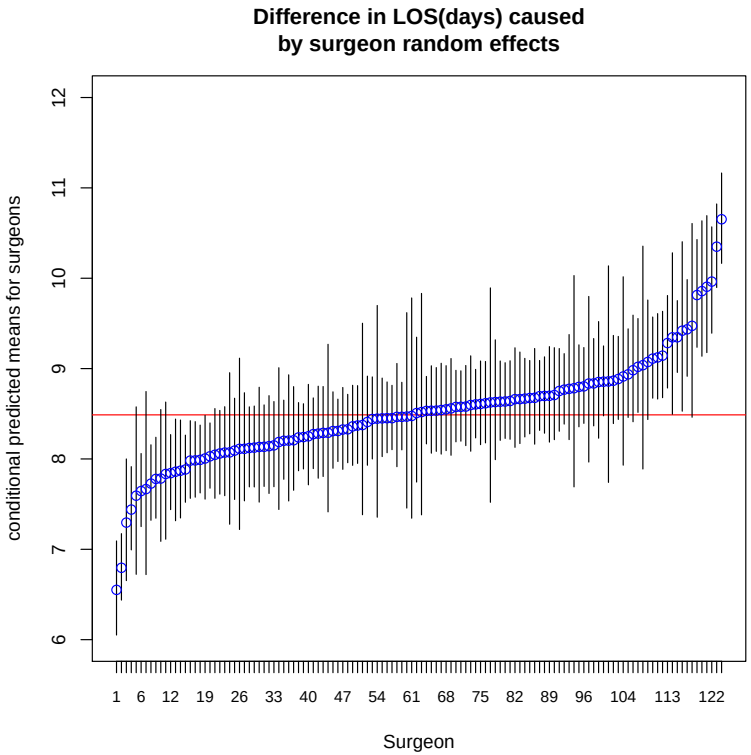
* Proportion of the variation in the outcome attributed to the Centre, surgeon, anaesthetist and the patient risk profile.

	Centre	***Surgeon***	***Anaesthetist***	***Patient***
ICC (%)	0	4.01	0.24	95.75

Table: Percentage of outcome variation due to each group

Patient vs. Process outcomes

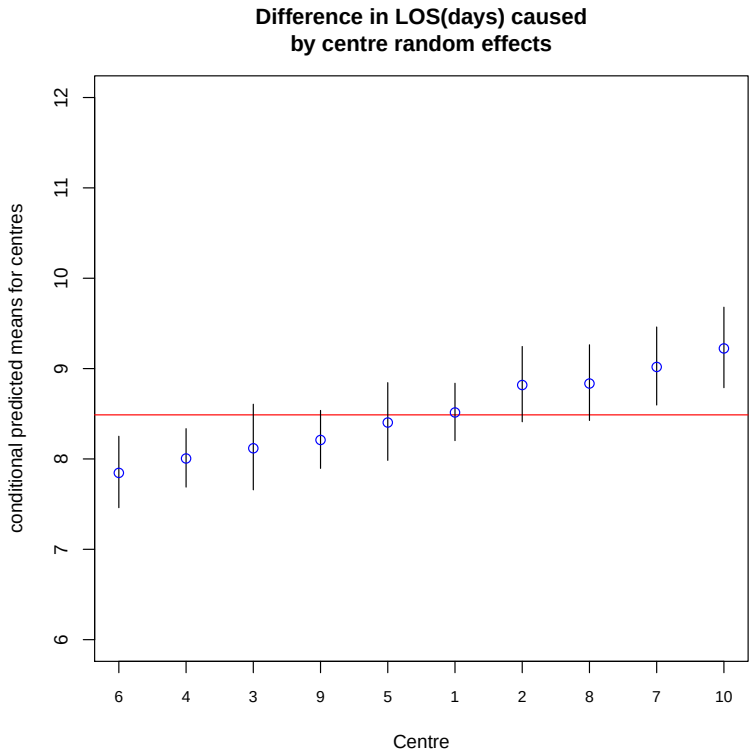
Mean LOS per Surgeon



(e) Surgeon "forest plot" adjusted for case-mix and both for Centre and Anaesthetist

$ICC_{S/A}$=2.79%

Mean LOS per Centre



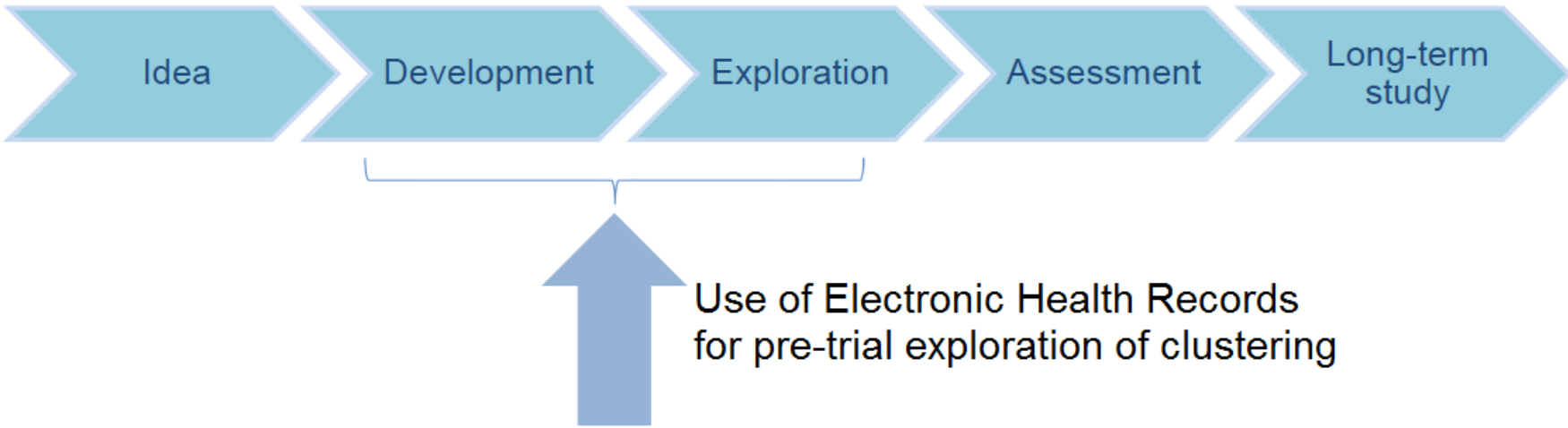
(f) Centre "forest plot" adjusted for case-mix and both for Surgeon and Anaesthetist

$ICC_{C/S,A}$=1.59%

Assessment of multiple surgical components

* **Identification of relevant setting and data sources**

↪ Limited information from RCTs on the effects of different intervention components at trial design.



↪ Examples of fit-for-purpose, large collaborative registries ⟶ UK Registry of Prostate Embolization (UK-ROPE) registry.

Choice of Trial design

Design Effect

Clustering Scenario	**Design Effect**
A) Main Component - Equal cluster sizes	$1+(\bar{m}_S\text{-}1)\rho_S$

Table: Design Effect for different clustering scenarios

$\bar{m}_S$,$\bar{m}_A$, the average number of patients treated per surgeon and anaesthetist.

cv_S,cv_A, the coefficient of variation per surgeon and anaesthetist.

ρ_S,ρ_A the $ICC_{surgeon}$, $ICC_{anaesthetist}$ respectively.

Choice of Trial design

Design Effect

Clustering Scenario	**Design Effect**
A) Main Component - Equal cluster sizes	$1+(\bar{m}_S\text{-}1)\rho_S$
B) Main component - Unequal cluster sizes	$1+(\bar{m}_S(1+cv_S^2)\text{-}1)\rho_S$

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Design Effect

Clustering Scenario	**Design Effect**
A) Main Component - Equal cluster sizes	$1+(\bar{m}_S\text{-}1)\rho_S$
B) Main component - Unequal cluster sizes	$1+(\bar{m}_S(1+cv_S^2)\text{-}1)\rho_S$
C) Cross-classification	$1+(\bar{m}_S(1+cv_S^2)\text{-}1)\rho_S+(\bar{m}_A(1+cv_A^2)\text{-}1)\rho_A$

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$\bar{m}_S$,$\bar{m}_A$, the average number of patients treated per surgeon and anaesthetist.

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Choice of Trial design

↪ Primary outcome: in-hospital death.

↪ $ICC_{surgeon}$=4.01%, $ICC_{anaesthetist}$=0.24%

Comparator	Design Effect		
	Main component Equal CS	Main component Unequal CS	Cross-classification
Surgery vs. Surgery	1.361	1.417	1.434
Surgery vs. Medical	1.180	1.209	1.217

↪ Power is underestimated if clustering is ignored.

↪ In this setting $ICC_{anaesthetist}$ very small ⇒ minimal differences in sample size inflation.

Conclusions

* *Cardiac surgery case-study*

- Surgeon expertise had a small, yet significant influence.
- In this setting, anaesthetist effect was negligible after adjusting for surgeon effects.
- Centre did not affect mortality after adjustment for surgeon and anaesthetist but did have an impact on LOS.
- Loss in power by ignoring anaesthetist-induced clustering minimal in this example.

Conclusions

* *Importance of Electronic Health Records*

- Construct databases of risk-adjusted estimates of ICCs for different intervention components.
- Use of evidence synthesis to enrich short-term RCT outcomes $\longrightarrow$ long-term cost-effectiveness analyses.
- Identify the presence of clustering for various outcomes of interest $\longrightarrow$ patient vs. process outcomes.

Conclusions

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- Identify the presence of clustering for various outcomes of interest $\longrightarrow$ patient vs. process outcomes.

Proposed Methodology

- enables the investigation of non-hierarchical data structures and the construction of ICC databases.
- informs the choice of trial design, comparator and sample size calculations.

References I

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Alternative approach: *GEEs*

Generalised Estimating Equations

- GEE assume observations in same cluster correlated but independent to observations from distinct clusters.
- Exchangeable correlation structure $\longrightarrow$ equivalent to a random intercept model.
- Standard errors robust to misspecification of the working correlation structure.

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Generalised Estimating Equations

- GEE assume observations in same cluster correlated but independent to observations from distinct clusters.
- Exchangeable correlation structure $\longrightarrow$ equivalent to a random intercept model.
- Standard errors robust to misspecification of the working correlation structure.

Inappropriate in this case

- Do not model explicitly between and within cluster variability.
- GEE correlation measure underestimated with few clusters available $\longrightarrow$ sub-optimal measure.
- Cannot be used to study specific cluster performance.

Anaesthetist performance

- Examine whether specific surgeon/anaesthetist collaborations instead of randomly assigning pairs improve collective performance.

- Anaesthetists $\Rightarrow$ "members" of more than one surgeon clusters.

- Interest: variation in anaesthetists' performance attributable to surgeons and its dependence on the partition of anaesthetic caseload across surgeons.
$\hookrightarrow$ *Variance Partition coefficient* (VPC).

- *ICC*: correlation between two anaesthetists depending on their surgeon collaboration profiles.

Anaesthetist Multiple Membership Multiple classification model

$$logit(\pi_i) = \beta_{0i} + \sum_w \beta_w (x_{iw} - \overline{x_w}) \quad (4)$$

$\beta_{0i} = \alpha + v_{A_{(i)}} + \sum_{j \in Sur_{(i)}} w_{i,j} u_j$.

Random intercepts' distributions: $u_j \sim N(0, \sigma_u^2)$ for the surgeon.

$v_{A_{(i)}} \sim N(0, \sigma_v^2)$ for the anaesthetist.

Choice of weights

Weights

$$w_{i,j} = \frac{operations\ done\ by\ A_{(i)}\ with\ Sur_{(i),j}}{total\ operations\ done\ by\ A_{(i)}}$$

$\hookrightarrow$ Fitted using simulation methods in package MCMCglmm in R.

Random Interaction

- Possibility of interacting operators within medical teams.
- Marginal effect of anaesthetist differs according to the operating surgeon and vice-versa.
- Need to extend the cross-classified model $\rightarrow$ term for additional random source of variation.

Application

Two-level cross-classification model with random interaction

$$logit(\pi_{ijk}) = \beta_{0ij} + \sum_{w} \beta_w (x_{ijkw} - \overline{x_w}) \tag{5}$$

where $y_{ijk}|\pi_{ijk} \sim Binomial(1, \pi_{ijk})$.

$\beta_{0ij} = \alpha + u_i + v_j + uv_{(i,j)}$, $u_i \sim N(0, \sigma_u^2)$ i^{th} surgeon random intercept
$v_j \sim N(0, \sigma_v^2)$ for the j^{th} anaesthetist
$uv_{(i,j)} \sim N(0, \sigma_{uv}^2)$ respectively for pair (i, j)

π_{ijk} the probability of an in hospital death for the k^{th} patient treated by the i^{th} surgeon and j^{th} anaesthetist.

$e_{ijk} \sim Logistic(0, 1) \Rightarrow \sigma_e^2 = \pi^2/3$

x_{ijkw} the w^{th} covariate for the k^{th} patient treated by the i^{th} surgeon and j^{th} anaesthetist.

Correlation Coefficients

Partition of variation

$$VPC = \frac{\sigma_u^2 \sum_{j \in Clust_{(i)}} (w_{i,j})^2}{\sigma_u^2 \sum_{j \in Clust_{(i)}} (w_{i,j})^2 + \sigma_e^2}$$

$$ICC = \frac{\sigma_u^2 \sum_{j \in Clust_{(i)} \cup Clust_{(k)}} w_{i,j} w_{k,j}}{\sqrt{\sigma_u^2 \sum_{j \in Clust_{(i)}} (w_{i,j})^2 + \sigma_e^2} \sqrt{\sigma_u^2 \sum_{j \in Clust_{(k)}} (w_{k,j})^2 + \sigma_e^2}}$$

Two-level model

$$VPC = ICC = \frac{\sigma_u^2}{\sigma_u^2 + \sigma_e^2}$$

Choice of Priors

- Random effects variance

$*$ $\Gamma^{-1}(\epsilon, \epsilon)$, $\epsilon \to 0$

$**$ Improper uniform on σ_u^2.

Drawbacks:

$*$ bad behaviour for variances close to 0.

$**$ miscalibration towards higher σ_u values and need more than 4 clusters to get a proper posterior.

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$*$ bad behaviour for variances close to 0.

$**$ miscalibration towards higher σ_u values and need more than 4 clusters to get a proper posterior.

$\hookrightarrow$ **Suggest**: Improper Uniform on σ_u.

$\hookrightarrow$ Parameter-expanded priors and slice sampling to ensure effective mixing.

Parameter Expansion

- Used in single-response models when a variance component is small and chain gets stuck at values close to zero.
- Originally applied to Gibbs sampling to speed up convergence and mixing properties of the chain.
- Achieved by introducing parameters α not identified in the likelihood, for which all information comes from the prior. Placing priors on these, induces different prior distributions for the variance components.
- All priors from the non-central scaled F distribution $\rightarrow$ prior for the standard deviation is a non-central folded scaled t-distribution (Gelman, 2006).
- Essential to specify the prior means $\alpha.mu$ and prior covariance $\alpha.V$ in the prior.

Slice Sampling

- Can be used when the distribution can be factored such that one factor is a distribution from which truncated random variables can be drawn.
- The latent variables in univariate binary models can be updated in this way.
- In these models, slice sampling is only marginally more efficient than adaptive Metropolis-Hastings updates when the residual variance is fixed.
- For parameter expanded binary models where the residual variance is not fixed, the slice sampler can be much more efficient.