

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

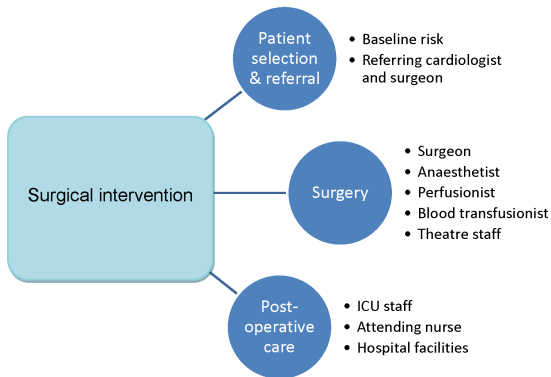
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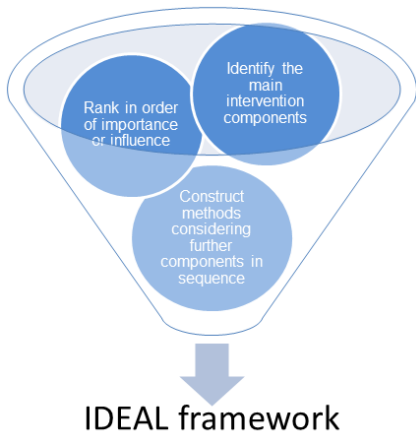
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Background

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



* **Building up** complex surgical evaluations:

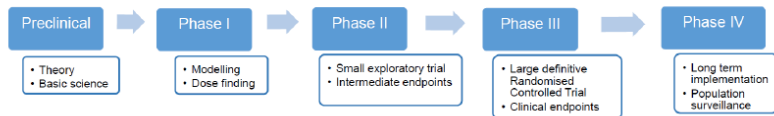


↪ Five-stage paradigm delineating the development of innovative surgical procedures.

Background

* IDEAL stages

(a) Five-phase pharmaceutical development framework



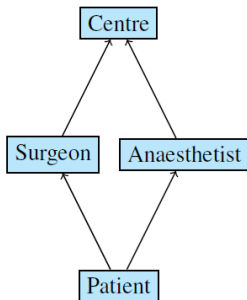
(b) The IDEAL framework stages



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

- ↪ 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
⇒ 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) → Proportion of variation in outcome attributed to:
 - Centre
 - Surgeons
 - Anaesthetists
 - Patients

Models:

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

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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.

- 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.

Three-level random intercept model

$$\text{logit}(\pi_{ijk}) = \beta_{0ij} + \sum_w \beta_w (x_{ijkw} - \bar{x}_w) \quad (1)$$

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

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

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

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

$$\text{logit}(\pi_{ijk}) = \beta_{0ij} + \sum_w \beta_w (x_{ijkw} - \bar{x}_w) \quad (2)$$

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

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

Three-level cross-classified model

$$\text{logit}(\pi_{ijkl}) = \beta_{0ijk} + \sum_w \beta_w (x_{ijklw} - \bar{x}_w) \quad (3)$$

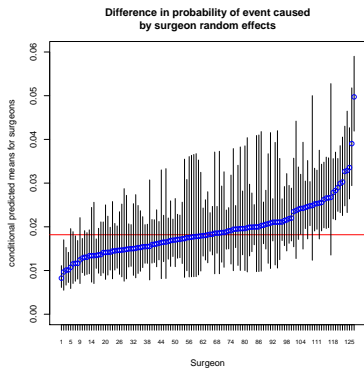
$\beta_{0ijk} = \alpha + u_{ij} + v_{ik} + z_i$, $z_i \sim N(0, \sigma_z^2)$ the i^{th} Centre random intercept.

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

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

Results

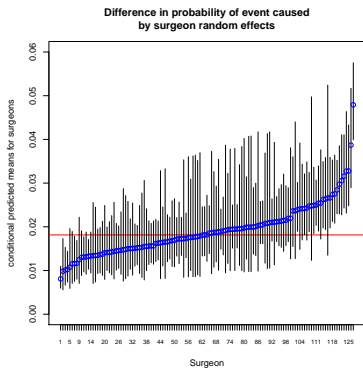
Three-level model



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

$$ICC_S=4.06\%$$

Three-level cross-classified model

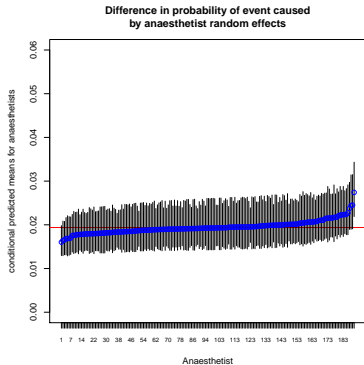


(b) Surgeon "forest plot" adjusted for case-mix and both for Anaesthetist and Centre

$$ICC_{S/A}=4.01\%$$

Results

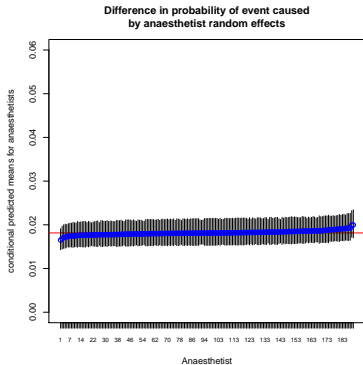
Three-level model



(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

$$ICC_{A/S} = 0.24\%$$

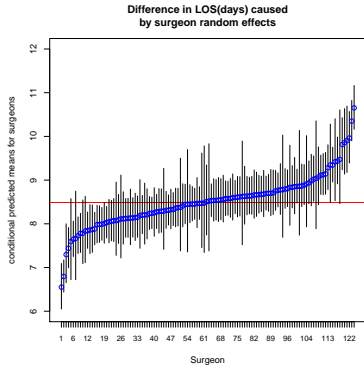
* Proportion of the variation in the outcome attributed to the Centre, surgeon, anaesthetist and the patient risk profile.

	<i>Centre</i>	<i>Surgeon</i>	<i>Anaesthetist</i>	<i>Patient</i>
<i>ICC (%)</i>	0	4.01	0.24	95.75

Table: Percentage of outcome variation due to each group

Patient vs. Process outcomes

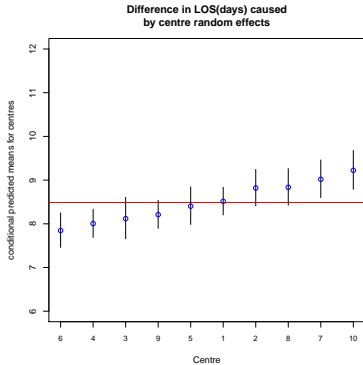
Mean LOS per Surgeon



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

$$ICC_{S/A}=2.79\%$$

Mean LOS per Centre



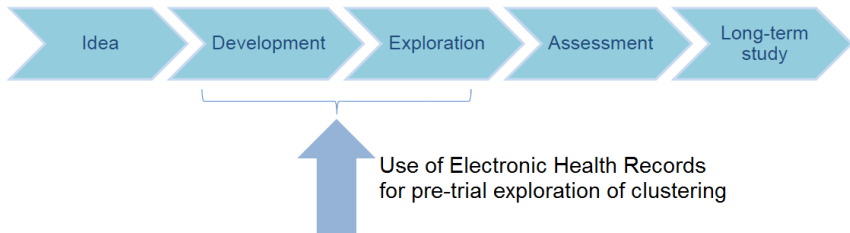
(f) Centre "forest plot" adjusted for case-mix and both for Surgeon and Anaesthetist

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

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	$1+(\bar{m}_S-1)\rho_S$

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	$1+(\bar{m}_S-1)\rho_S$
B) Main component - Unequal cluster sizes	$1+(\bar{m}_S(1+cv_S^2)-1)\rho_S$

Table: Design Effect for different clustering scenarios

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Design Effect

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

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

↪ Primary outcome: in-hospital death.

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

Comparator	Design Effect		
	Main component	Main component	Cross-classification
	Equal CS	Unequal CS	
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 \Rightarrow minimal differences in sample size inflation.

* 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.

* 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 → long-term cost-effectiveness analyses.
- Identify the presence of clustering for various outcomes of interest → patient vs. process outcomes.

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 → long-term cost-effectiveness analyses.
- Identify the presence of clustering for various outcomes of interest → 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.

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Generalised Estimating Equations

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

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Inappropriate in this case

- Do not model explicitly between and within cluster variability.
- GEE correlation measure underestimated with few clusters available → 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

$$\text{logit}(\pi_i) = \beta_{0i} + \sum_w \beta_w (x_{iw} - \bar{x}_w) \quad (4)$$

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

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.

Weights

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

↪ 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 → term for additional random source of variation.

Two-level cross-classification model with random interaction

$$\text{logit}(\pi_{ijk}) = \beta_{0ij} + \sum_w \beta_w (x_{ijkw} - \bar{x}_w) \quad (5)$$

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

$\beta_{0ij} = \alpha + u_i + v_j + uv_{(i,j)}$, $u_i \sim N(0, \sigma_u^2)$ 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.

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

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

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

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

Two-level model

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

Choice of Priors

- Random effects variance

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

- ** 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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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.

↪ **Suggest:** Improper Uniform on σ_u .

↪ 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.