The importance of post-discharge surgical site infection surveillance: an exploration of surrogate outcome validity in a global randomised controlled trial (FALCON)

Surgical site infection (SSI) is the most common complication of abdominal surgery worldwide and was recognised as the highest priority research area in surgery in a global consensus process.[1] The accepted gold standard for diagnosis of SSI is in-person evaluation according to US Centers for Disease Control and Prevention criteria.[2] This requires a patient to travel back to hospital for a face-to-face evaluation at 30 days postoperatively. This is problematic for several reasons in low-income and middle-income countries (LMICs); first, patients might have to travel very long distances; second, patients already face risk of catastrophic expenditure from surgery; third, there is wide variability in discharge pathways and antibiotic prophylaxis between centres; and fourth, there is high opportunity cost where the surgical workforce is scarce.[3] In-hospital SSI assessment (ie, just before a patient is discharged) is therefore an attractive alternative for global randomised controlled trials (RCTs). It could reduce resource use, provide outcome data earlier, and improve efficiency. However, in-hospital SSI assessment would need to be a valid surrogate to ensure research quality and minimise risk of bias.

Surrogate outcomes can be assessed against four Prentice criteria:[4] (1) treatment must have an effect (whether significant or non-significant) on the surrogate endpoint (ie, in-hospital SSI); (2) treatment must have a similar effect (whether significant or non-significant) on the true endpoint (ie, 30-day SSI); (3) the surrogate endpoint (in-hospital SSI) must have an effect on the true endpoint (ie, 30-day SSI); (4) the full effect of treatment on the true endpoint (30-day SSI) must be mediated by the surrogate (ie, in-hospital SSI). These criteria have been updated to provide a statistical approach to assessment of surrogacy in binary-binary endpoints.[5]

To explore the validity of in-hospital SSI assessment as a surrogate for 30-day SSI assessment, we performed a secondary analysis of the FALCON trial.[6] This was a pragmatic 2 × 2 factorial stratified RCT evaluating skin preparation and coated sutures in 5788 patients from seven LMICs. Patients underwent both in-hospital and 30-day SSI assessment. In this study, 311 (5·4%) of 5788 patients died before 30 postoperative days (232 missing data). Of 5245 patients alive at 30 days, 43 (0·8%) remained in hospital (118 missing data) and there was very high SSI rate in this group (62·8%, 27/43). Of those who were discharged and alive at 30 days after surgery (n=5084, included in this analysis) the median timing of discharge was 5 days (IQR 3–8). The SSI rate was 12·0% (611/5083, 1 missing) at hospital discharge and 20·2% (1025/5084) at 30 days. Overall, 414 (40·4%) of the total 1025 SSIs occurred after discharge. The effectiveness of the FALCON trial interventions by contamination strata for 30-day SSI and in-hospital SSI are presented in the appendix (p 1); there were no clinically significant differences in the effect estimates or directionality.

We used an information-theoretic approach to estimate trial-level and individual-level surrogacy based on full fixed-effect models. We created subgroups by country to allow meta-analysis[7] (R version 4.2.1, package: *surrogate*). Within-trial correlation (the extent to which the surrogate [in-hospital SSI] estimates the magnitude and variability of the effect estimate between trial groups in comparison to the true endpoint [30-day SSI]) can be explored using the slope of the linear regression between the trial-level effects of treatment on both endpoints (R^2_{trial}). A surrogate would be "trial valid" if the R^2_{trial} was close to 1. Within-patient association (the extent to which occurrence of the surrogate [in-hospital SSI] is predictive of the true endpoint [30-day SSI]) can be explored with the individual-level association between both endpoints ($R^2_{b.individual}$). A surrogate would be "individual valid" if the $R^2_{b.individual}$ was close to 1 (eg, ≥0·8).[7] Both criteria must be met for a surrogate to be valid overall.

The R^2_{trial} and $R^2_{b.individual}$ for in-hospital SSI assessment in the FALCON trial for patients who were discharged and alive at 30 days after surgery are summarised in the figure. The model specification and output are presented in full in the appendix (pp 12–14). The R^2_{trial} was 0·69 (95 CI 0·20–0·95) for skin preparation groups, the R^2_{trial} was 0·44 (0·03–0·85) for the fascial suture groups, and the $R^2_{b.individual}$ was 0·65 (0·63–0·67). This indicates that in-hospital SSI is not a valid surrogate for 30-day SSI. The wide variation in trial-level surrogacy from country to country might have reflected differences in discharge practices between countries.

Together these data suggest that in-hospital SSI assessment is not a valid surrogate for 30-day SSI in multinational RCTs. Although early and late manifestation of SSI can be influenced by different biological mechanisms and perioperative processes (such as duration of antimicrobial prophylaxis), robust post-discharge surveillance pathways are required for high-quality research studies; this has been recognised as a key quality measure in an adapted Cochrane Risk of Bias-2 (ROB-2) tool for SSI research.[8] Although these findings are specific to one postoperative complication, they highlight the need for robust

See Online for appendix

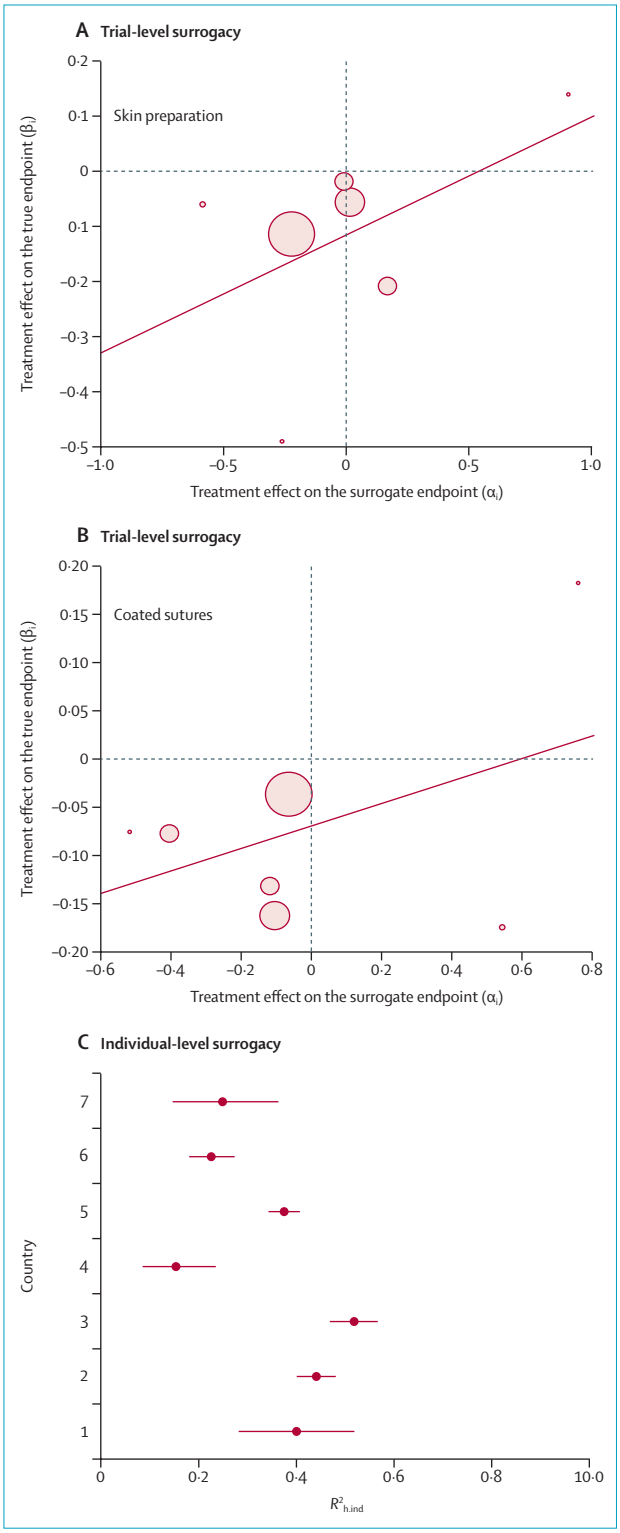

Figure: **Trial-level and individual-level surrogacy effects in the FALCON trial data**
Each estimate plotted for the R^2 coefficient represents the slope of the linear regression plotted between the surrogate and true endpoint for each different country participating in the FALCON trial.

evaluation of follow-up methods when implementing randomised trials across diverse health systems.

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