would facilitate the use of miRNA-based screening strategy in clinical settings.

Disclosure: The authors declare no conflicts of interest.

Kecheng Zhang, MD
Lin Chen, MD
Department of General Surgery, People's Liberation Army General Hospital
Beijing, China
chenlin@301hospital.com.cn

REFERENCES

1. Carter JV, Roberts HL, Pan J, et al. A highly predictive model for diagnosis of colorectal neoplasms using plasma microrna: improving specificity and sensitivity. *Ann Surg*. 2016;264: 575–584.
2. Dong H, Lei J, Ding L, et al. MicroRNA: function, detection, and bioanalysis. *Chem Rev*. 2013;113: 6207–6233.
3. Moldovan L, Batte KE, Trgovcich J, et al. Methodological challenges in utilizing miRNAs as circulating biomarkers. *J Cell Mol Med*. 2014; 18:371–390.
4. Schultz NA, Dehlendorff C, Jensen BV, et al. MicroRNA biomarkers in whole blood for detection of pancreatic cancer. *JAMA*. 2014;311:392–404.
5. Zhu C, Ren C, Han J, et al. A five-microRNA panel in plasma was identified as potential biomarker for early detection of gastric cancer. *Br J Cancer*. 2014;110:2291–2299.

Drain After Pancreatoduodenectomy: Methodological Issues

To the Editor:

The *Annals of Surgery* have recently published 2 interesting articles addressing routine use of intraabdominal drains after pancreatoduodenectomies (PD).[1,2] Both articles provide significant insight into the clinical dilemma under scrutiny but they also demonstrate some equally interesting methodological issues. The PANDRA trial, a randomized controlled trial (RCT), included only 13% of eligible patients and 40 patients in the no-drain group had drains placed because of surgeons deliberately violating trial protocol.[1] Both issues are known Achilles heels of randomized trials in surgery.[3] The low fraction of eligible patients that were included severely threatens external validity (generalizability) of trial results. The 2-center trial by McMillan et al[2] used a prospective (nonrandomized) cohort design. As long as complete series are ensured and the trial outcome is predefined, robust, and easy to score, this is a powerful design. The risk of biased selection is almost completely avoided by consecutively including all patients, incomplete blinding is never an issue and optimal external validity ensured.[3] The magnitude of effect 'across the nation' is also much better preserved in the design used by McMillan's trial and this is an evidence modality that has received too little attention compared with evidence of 'cause-and-effect' that is the *raison d'être* of the explanatory RCT.[3]

The devastating number of trial violations in the German trial illustrates lack of surgeon equipoise immediately after resection and shows that the timing of randomization was wrong.[1] We have previously conducted a large RCT on intraoperative insertion of feeding catheters and anticipated this phenomenon.[4] Postresection randomization performed by computer from the operating theatre immediately before closure of the abdomen is effortless today and would have avoided this problem in the PANDRA trial.

Disclosure: The author declares no conflicts of interest.

Kristoffer Lassen, MD, PhD
Oslo University Hospital, Oslo, Norway.
xtofero@gmail.com; krlass@ous-hf.no.

REFERENCES

1. Witzigmann H, Diener MK, Kienkotter S, et al. No need for routine drainage after pancreatic head resection: the dual-center, randomized, controlled PANDRA trial (ISRCTN04937707). *Ann Surg*. 2016;264:528–537.
2. McMillan MT, Malleo G, Bassi C, et al. Multicenter, prospective trial of selective drain management for pancreatoduodenectomy using risk stratification. *Ann Surg*. 2016 [Epub ahead of print].
3. Lassen K, Høye A, Myrmel T. Randomised trials in surgery: the burden of evidence. *Rev Recent Clin Trials*. 2012;7:244–248.
4. Lassen K, Kjaeve J, Fetveit T, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Ann Surg*. 2008; 247:721–729.

OPEN

Questions Regarding Statistical Inferences, Quality of Life, and Conclusions From the COBRA Study

To the Editor:

As the Chief Medical Officer (RS) and Head of Health Economics and Outcomes Research (DM) for ACELITY, we acknowledge and value addressing the ''clinical data gap'' in ventral hernia repair.[1] We believe it is equally important that studies are conducted and reported with appropriate methodological rigor. The aim of our letter is to provide surgeons and other study reviewers a deeper and clearer understanding of the recently published complex open bioabsorbable reconstruction of the abdominal wall (COBRA) study. In particular, we highlight the limitations of the study design employed, the limitations in the statistical analysis and reporting, and the inappropriateness of the conclusions drawn by the authors. To be clear, W.L. Gore & Associates, the sponsor of The COBRA study, and LifeCell, an ACELITY Company, are competitors, and it would be disingenuous not to explicitly declare this before reviewing the aforementioned study. Our hope is that this critical assessment might assist surgeons in their evaluation of this and future studies.

The stated objective was to evaluate the use and performance of a new tissue reinforcement material. The absence of a control group precludes statements attributing treatment effect to the mesh. In a single-arm trial, evaluating new mesh reinforcement cannot be separated from the surgical treatment effect.[2] Other variables, both measured (surgical technique, mesh placement, presence of infection, enrollment criteria, size of wound) and unmeasured (surgeon experience, care pathways, time) all have a substantial effect on response to treatment and importantly are all uncontrolled. As a result, from the outset, the objective of evaluating a new mesh was incongruent with a single-arm design.

The sample size was calculated from a background event rate of 50% recurrence at 2 years, based on the study by de Vries Reilingh et al,[3] which recruited patients between 1999 and 2001, a full 12 to 13 years before the COBRA study. Moreover, the defect size was ~2 times larger in the study by de Vries Reilingh et al. Differences in patient characteristics from the original study, and advances in surgical technique and patient care strategies in the intervening time would suggest that 50% recurrence is inappropriate for the current timeframe and study. This likely underestimates the necessary sample size for an informative study and of its relevance to current practice.

The purpose of statistical inference is to use a sample of patients to draw conclusions

about the larger population from which the sample was taken. A commonly reported metric in this regard is the 95% confidence interval (CI), and its absence from Fig. 1[1] makes interpretation difficult. For example, ''a wide confidence interval points to a lack of information'' and the potential for overinterpreting these findings.[4]

Health-related quality of life (HRQoL) is also critically important, and this study attempted to provide insights in an area of increasing interest in ventral hernia. Analysis of HRQoL presents some unique challenges because multiple instruments are collected at multiple time points; thus, missing data are inevitable. How missing data were handled was not described (strengthening the reporting of observational studies in epidemiology checklist referred to by this journal),[5] nor did the statistical testing methodology consider adjustments for multiple testing and repeated measures over time. In addition, the minimum clinically important difference (MCID) needs to be considered since statistical significance may be so small as to be clinically irrelevant.[6] Clinicians are interested in HRQoL that would be considered meaningful or beneficial by the patient.[7] Conversely, statistical significance leaves unanswered questions about clinical relevance of the changes. Therefore, the authors missed an opportunity to provide insights regarding changes important to patients. Finally, and perhaps most importantly, as stated earlier, these changes cannot be attributed to any single variable, the mesh in particular.

Inferences and conclusions are inextricably linked to the study design, thus; it is surprising to see statements of comparison with other materials and a failure to recognize differences in patient characteristics, that is, beyond the technique. The defect size in repair of infected or contaminated ventral incisional hernias (RICH) was substantially larger at 236 versus 137 cm^2, and 64% (RICH) versus 45% (COBRA) of the patients had a prior recurrent/previous hernia; thus the statement that 1 study had a lower rate compared with the other is overstated and inappropriate. Moreover, attribution of effect to the mesh is incorrect and references to variables not measured are inappropriate extrapolations. Concluding statements that do not reflect the data that was assessed, reach beyond the study design, or extend outside the current body of evidence become a disservice to the surgeons seeking to improve the care of their patients.

Again addressing clinical data gaps is critically important for the surgeons that use these products and those patients who receive them. LifeCell has actively engaged and supported the American Hernia Society Quality Collaborative initiative and also championed similar efforts outside of the United States in an effort to develop additional clinical data and understand long-term outcomes in ventral hernia globally. The success of these efforts demands that we not only understand the data, but have keen interest in the methods and their limitations.

Disclosures: DM and RS are both employees of ACELITY.

David Macarios, MBA, MSc
Health Economics and Outcomes Research,
ACELITY, Bridgewater, NJ
David.Macarios@acelity.com

Ronald P. Silverman, MD, FACS
Division of Plastic Surgery, University of
Maryland School of Medicine
Baltimore, MD
Global Medical, ACELITY
San Antonio, TX

REFERENCES

1. Rosen MJ, Bauer JJ, Harmaty M, et al. Multicenter, prospective, longitudinal study of the recurrence, surgical site infection, and quality of life after contaminated ventral hernia repair using biosynthetic absorbable mesh. The COBRA study. *Ann Surg*. 2015 [Epub ahead of print].
2. Evans SR. Clinical trial structures. *J Exp Stroke Transl Med*. 2010;3:8–18.
3. de Vries Reilingh TS, van Goor H, Charbon JA, et al. Repair of giant midline abdominal wall hernias: 'components separation technique' versus prosthetic repair: interim analysis of a randomized controlled trial. *World J Surg*. 2007;31:756–763.
4. Altman DG, Gore SM, Gardner MJ, et al. Statistical guidelines for contributors to medical journals. *Br Med J*. 1983;286:1489–1493.
5. No Authors. Annals of Surgery Online Submission and Review System [Website]. Available at: http://edmgr ovid com/annsurg/2016; http://edmgr.ovid.com/annsurg/accounts/ifauth.htm. Accessed September 8, 2016.
6. McCrum-Gardner E. Sample size and power calculations made simple. *Int J Ther Rehabil*. 2010;17:10–14.
7. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989; 10:407–415.

Reply to Letter to The Editor Regarding the COBRA Trial: What Will it Take to Perform High-quality Hernia Research?

Reply:

The authors of the COBRA trial would like to thank Mr Macarios and Dr Silverman for their insightful comments regarding our recent publication.[1] As they point out, the lack of a control group limits any firm conclusions as to the effect of the device on the outcomes that we measured in the study, and that was clearly listed as a limitation in the discussion. We would, however, point out that this study represents the first scientific investigation of a bioabsorbable mesh in the setting of complex abdominal wall reconstruction. Given that there are no prior publications to help guide our expected outcomes, we did feel that a single-arm prospective study in a well-defined patient population has significant merit as a first step, and hopefully will be used to appropriately power future randomized controlled trials with appropriate comparison groups. In fact, the original study of Acelity's biologic mesh, Strattice, was performed in a similar manner as a prospective single-arm study in a similar patient population.[2] Unfortunately, there was no further investigation into the actual effect of the device versus all of the other contributing factors with a well-designed trial.

We do believe the statistical methods used in our paper have been clearly stated and provide readers with a clear evaluation of the study results. The authors make the claim that, due to assumptions made in the computation of sample size, the study ''likely underestimates the necessary sample size for an informative study and of its relevance to current practice." A critical distinction should be made between the assumptions used to determine sample size versus the utility of the actual sample size of the study. Once the study has been designed, the assumptions used to create the sample size of the study are no longer pertinent to the conduct and interpretation of the study itself. It is thus important to remind the reader that the resulting study was comprised of 104 subjects; these subjects were followed in a multicenter study for 2 years, with a standardized, prespecified protocol. The goal of this study was not a definitive evaluation of bioprosthetic materials, but rather was a hypothesis-generating evaluation. With regards to the presentation of confidence intervals in our Kaplan-Meier curves, we did note that in the RICH manuscript, 95% confidence intervals were not presented either.[2] However, to clarify this, we have provided the 95% confidence intervals for our manuscript here. In addition, these estimates, like all Kaplan-Meier estimates, account for subjects lost to follow-up during the course of the study.

Time Point	Recurrence Rate	95% Confidence Interval
1 mo	0.0%	
6 mos	3.0%	(1.0%, 9.1%)
12 mos	9.4%	(5.0%, 17.3%)
24 mos	17.3%	(11.0%, 26.8%)