We would therefore like to suggest an addition to the WireSafe kit. We feel that the WireSafe kit may be enhanced by including preloaded "flush" syringes within the locked kit. This will ensure that the guidewire is always removed before the lumens are flushed. For those that prefer to prime the lumens of their central lines before insertion, perhaps a 3-ml preloaded, color-coded syringe clearly marked as "priming solution" could be included within the pack but outside of the locked kit. We believe a forced brake before flushing the central line lumen may prevent a removable guidewire from becoming a "lost" or retained one.

Competing Interests

The authors declare no competing interests.

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In Reply:

We would like to thank Camporesi *et al.* for their interest in the locked procedure pack (WireSafe) and our article. They are, of course, absolutely correct that the WireSafe is not intended to prevent guidewire breakage or malfunction; however, in our simulation it was shown to be highly efficacious in preventing clinicians simply forgetting to remove the whole guidewire.[1] We see these as two separate problems requiring two separate solutions. Guidewire fracture or impingement due to kinking or unraveling needs to be addressed with improvements in manufacturing, materials, and operative technique. However, whole guidewire retention due to forgetfulness requires an understanding of human factors science and the inevitable fallibility of human operators, made worse by suboptimal working conditions. The well-recognized success of the energy, transportation, and other high-reliability industries use system changes and fail-safe forcing functions engineered into equipment design to prevent rare, but serious, errors and these are tested in a simulation setting. The incidence we quoted was from the article by Vannucci *et al.*, referring to whole guidewire retention due to forgetfulness, and was 1:3,291.[2] Interestingly, the incidence for "operator distraction" from the article by Omar *et al.* was almost identical at 1:3,221.[3] These concordant figures would equate to approximately four forgotten guidewires everyday in the United States (an estimated 5,000,000 central venous catheters are placed annually[2]). A recent article evaluating 391 cases from the U.S. Veterans Health Administration also supported the incidence of forgotten guide wires in the United States, and in addition, showed that 91% were whole—rather than fractured—guidewires.[4] Regarding statistical significance for rare events in routine clinical practice, as discussed in our article, studies can seldom be powered to achieve significance.

Awareness and educational programs alone may have a higher cost and a more limited impact in the long term than design improvement. In the United Kingdom, the National Health Service England database contains 237 cases of forgotten whole guidewires (2004 to 2015).[5] Despite being made a never event and increasing educational efforts in the National Health Service, the reported incidence has been increasing.[5] Although immediate documentation of removal is commendable, we note that in one of the cases reported by Vannucci *et al.*, guidewire removal was documented when it had, in fact, not been removed,[2] and we have observed this occurring in the National Health Service.

We strongly disagree that comparable reductions would be seen by educational programs and improving documentation alone. Short-term improvements are often seen, but the negative effects of associated cost, increased cognitive load, creeping complacency, and warning fatigue blight these programs. An engineered (forcing function) safety solution delivers a sustained effect over time and if detected immediately, forgotten guidewires are normally amenable to bedside removal.

We also thank Drs. Kapoor and Mayall for their particularly perceptive letter addressing a loophole, about which we have agonized, relating to guidewires being flushed into the circulation. As described above, this would affect a small minority of these never events as the guidewire remains within the catheter at the time of the postoperative x-ray in the majority,[5] and may migrate thereafter. Therefore, this should not discourage hospitals from using this solution. Our plan to use prefilled syringes was thwarted by the requirement of ethylene oxide, rather than gamma sterilization, by current packing companies; the former changes the pH and composition of saline in plastic sealed syringes. To prevent this, the WireSafe is sized to include a glass ampoule, an ampoule breaker, and a syringe with a filter needle, and we continue to try to influence packing companies to provide, and end users to request, these features. Additionally, we are aware of one company that is in the final stages of producing an ethylene oxide–compatible saline syringe, which we would endorse the use of within the WireSafe.

Competing Interests

Dr. Young has patented and is the inventor of the Venner WireSafe based on the locked pack described in this letter.

Dr. Mariyaselvam has been selected as a National Health Service Innovation Accelerator Fellow and National Health Service Clinical Entrepreneur Fellow to support the implementation of the Venner WireSafe. Both have ownership rights to the intellectual property and hope to be involved with supporting and advising on the commercialization of the Venner WireSafe, and may benefit financially alongside its clinical success, subject to future negotiation and agreement.

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Pharmacokinetic Pharmacodynamic Perspective on the Detection of Signs of Neural Inertia in Humans

To the Editor:

We read with great interest the paper, "Investigation of Slow-wave Activity Saturation during Surgical Anesthesia Reveals a Signature of Neural Inertia in Humans" by Warnaby *et al.*[1] The authors claim to have found experimental evidence for neural inertia in humans on the basis of a difference in the modeled slow-wave activity between induction and emergence from propofol anesthesia. As the authors state, until recently, neural inertia has only been observed in animals,[2] and evidence was lacking on the importance of this phenomenon in humans.

In parallel to Warnaby *et al.*, our group recently conducted a clinical study to investigate this phenomenon in healthy volunteers.[3] Our analysis suggested, among other things, that the ability to detect signs of neural inertia depends on the design of the study. Inspired by the work of Warnaby *et al.,* we would like to show how the drug titration scheme may influence the detection of neural inertia and could lead to false positive results.

In studies with anesthetic agents, effect-site target-controlled infusion is frequently used to control delivery of the drug. Effect-site target-controlled infusion systems calculate the optimal infusion regimen required to achieve the target effect-site concentration as fast as possible. These systems depend heavily on population pharmacokinetic models and their associated estimate for the rate-constant for equilibration between the plasma and effect-site concentrations. Clinical trial design is usually optimized with respect to this rate-constant for equilibration, such that pharmacodynamic endpoints are measured only after the predicted effect-site concentrations have reached a steady-state. The rate-constant for equilibration of $0.260\ min^{-1}$ integrated into the Diprifusor system (AstraZeneca Ltd., United Kingdom) suggests a rapid effect-site equilibration. Presumably based on this knowledge, Warnaby *et al.* chose to change the target effect-site every 2 min during the induction phase of the study. For the emergence phase, the authors simply stopped the propofol infusion.

However, reported rate-constants for equilibration in the literature vary substantially. For example, for propofol-induced changes in Bispectral Index (Covidien, USA), reported rate-constants for equilibration range between $0.17\ min^{-1}$[4] and $0.79\ min^{-1}$.[5] In our opinion, this uncertainty should be taken into account when designing a study; failing to do so may lead to false conclusions.

To substantiate our claim, we simulated the propofol infusion scheme used by Warnaby *et al.* (details with respect to the propofol infusion are found in the supplementary materials from an earlier paper from the same group[6]). Hereto, the Marsh model[7] and the associated rate-constant for equilibration of $0.260\ min^{-1}$ were used to calculate predicted arterial and effect-site concentrations. Predicted effect-site concentrations (C_e) were used to calculate a hypothetical drug effect according to equation 1 with a gamma (γ) and a concentration producing half-maximum effect (C_{50}) which were 2 and 1.5 μg/ml, respectively.

$$Effect = \frac{C_e^{\gamma}}{C_e^{\gamma} + C_{50}^{\gamma}}$$

Subsequently, the model in equation 1 was fitted to the simulated data for the induction and emergence phase separately to estimate the γ and C_{50}. This process was repeated with different values for the rate-constant for equilibration. Besides the study design described by Warnaby *et al.,* we also evaluated the drug infusion scheme that was used in our study.[3]

The results of the simulations are shown in figure 1. This figure clearly shows that the C_{50}s for induction and emergence depend on the rate-constant for equilibration. More specifically, if the wrong rate-constant for equilibration is used, the estimated C_{50} for induction increases, whereas that for emergence decreases. For example, in Warnaby *et al.,* a 30% difference between estimated induction and emergence C_{50} is expected when the rate-constant for equilibration is $0.160\ min^{-1}$, but none if it is $0.260\ min^{-1}$. Thus, neural inertia is an apparent artefact of the experiment. In addition,