Author’s response to reviews

Title: Effect of intermediate care on mortality following emergency abdominal surgery. The InCare-trial: rationale, design and feasibility of a randomised multi-centre trial.

Authors:

Morten Vester-Andersen (drvester@dadlnet.dk)
Tina Waldau (tina.waldau@regionh.dk)
Jørn Wetterslev (wetterslev@ctu.rh.dk)
Morten H Møller (mortenhylander@gmail.com)
Jacob Rosenberg (jacob.rosenberg@regionh.dk)
Lars N Jørgensen (larsnjorgensen@hotmail.com)
Inger Gillesberg (inger.gillesberg@regionh.dk)
Henrik L Jakobsen (henrik.loft jakobsen@regionh.dk)
Egon G Hansen (egon.godthaab.hansen@regionh.dk)
Lone M Poulsen (lmp@regionsjaelland.dk)
Jan Skovdal (jask@regionsjaelland.dk)
Ellen K Søgaard (ekso@regionsjaelland.dk)
Morten Bestle (mbes@noh.regionh.dk)
Jesper Vilandt (jevi@noh.regionh.dk)
Iben Rosenberg (iro@noh.regionh.dk)
Rasmus E Berthelsen (rasmuseb@dadlnet.dk)
Jens Pedersen (jens.pedersen@vest.rm.dk)
Mogens R Madsen (mogmad@rm.dk)
Thomas Feurstein (Thomas.feuerstein@shs.regionsyddanmark.dk)
Malene J Busse (malene_just@hotmail.com)
Johnny D.H. Andersen (johnny.andersen@shs.regionsyddanmark.dk)
Christian Maschmann (c.maschmann@dadlnet.dk)
Morten Rasmussen (mo.rasmussen@dadlnet.dk)
Christian Jessen (jessen_chr@hotmail.com)
Lasse Bugge (lasse.bugge@slb.regionsyddanmark.dk)
Helle Ørding (helle.oerding@slb.regionsyddanmark.dk)
Ann M Møller (ann.moeller@regionh.dk)

Version: 3 Date: 14 January 2013

Author’s response to reviews: see over
Dear Editor-in-chief

Thank you for inviting us to submit a revised version of our manuscript entitled “Effect of intermediate care on mortality following emergency abdominal surgery. The InCare-trial: rationale, design and feasibility of a randomised multi-centre trial.” We have carefully revised the manuscript, taking into account the comments made by the reviewer. All changes have been highlighted in yellow. Responses to the comments are detailed below.

The authors present a clear protocol. There are some issues that could benefit from clarification, as follows:

1. The randomisation takes place when the patient is ready for transfer to the surgical ward within 24 hours of surgery - subject to the availability of an IC bed. The authors indicate that there are 7 ICU beds per 100,000 Danes, but only 1.3 intermediate care beds. The protocol states that if no bed is available, then the patient is not randomised - couple of points:

a. how often is this happening? The authors indicate that with less than half the 400 target completed, the inclusion criteria of an APACHE score was reduced to 10, suggesting recruitment was slow? Unfortunately, this exclusion criterion is necessary because of the limited availability of intermediate/ intensive care beds at the trial-sites. This exclusion criterion does contribute to a slower recruitment than anticipated combined with a delayed trial initiation on two trial-sites. We agree that it is important to report how often participants are not enrolled because of “no bed is available”, and it will be reported in the result publication.

b. But as well as slow recruitment, there are the issues of generalisability and implementability. Generalisability because if at busy times more patients are turned away, there may be a selection bias for busy vs. quieter times? The authors indicate that they will collect mortality data on those eligible but not randomised, which is useful - but they should perhaps consider splitting this between those who refused to take part and those that were willing but no bed was available?

We agree that the exclusion criterion may compromise generalisability of the trial if this happens too often. To address this we plan to report mortality data on those eligible but not randomised. This will be done separately for participants willing to participate, but not randomised because no available bed. This has been clarified on page 13.

We do not believe that the exclusion criterion will lead to a selection bias as the participants are not randomised before all inclusion and exclusion criteria have been evaluated. Furthermore, the
randomisation is centralised using a telephone-based interactive-voice-response-system ensures adequate allocation concealment.

c. And implementability because if there are many fewer beds than are needed to even maximise the recruitment into the trial, how useful will the intervention be in practice if proved to be safe and effective?

We believe that if the intervention is proved to be safe and if an effect is shown on mortality it will be difficult for health-care providers not to allocate additional funds for the area. Further, if the intermediate care intervention is superior among the patients having access to an intermediate bed this at least will reflect a benefit that could be immediately implemented in everyday practice without allocating further resources to these patients. However, if the effect turns out to be smaller than anticipated, or absent, and ends up statistically non-significant this may be because too few patients participated in the trial and does not necessarily reflect absence of effect.

d. It would be useful to describe how many intermediate care beds each of the 7 participating hospitals had, and what there availability was during the trial to date, and whether ICU beds could be used, and how the provision of this IC beds in these 7 hospitals compares with (a) the rest of Denmark (they mention n=23 units total) and (b) other healthcare settings?

The intermediate care bed can be situated at an intermediate care, intensive care or a post-anaesthesia care unit, which can provide the intervention, if there is an available bed. This has been clarified on page 8.

We agree that the availability of intermediate care and intensive care beds per capita in the 7 trial-sites would be informative. Unfortunately the Danish public health-care system has been through extensive reform of the hospital structure during the last 4 years. This makes it impossible to provide reliable availability numbers from the 7 trial sites, as their intake area and number of ICU beds has changed several times during the trial. Furthermore the trial-sites were launched consecutively during the trial with 16 months between the first and the last launched trial-site. ICU availability per capita in 2005 in The US and UK is respectively 20 per 100.000 and 3.5 per 100.000 is provided on page 6 [1]

2. The tables listing what comprises IC and standard surgical ward care are very useful - they show that some components are the same, others quite different in terms of frequency and method of measurement. But what of the staff involved?

To what extent would any difference seen between the two randomised groups be down to differently experienced and skilled staff between IC and surgical ward sites? Is this something the authors will try to tease out or do they see this as an integral part of the package of care?

We have decided to define intermediate care (IC), as a minimal monitoring level and maximal treatment level which the involved units should be able to provide to participate in the trial. We did not demand that the staff assigned to the IC bed should have a certain level of education (i.e. ICU nurse) as we wanted surgical intermediate care units to be able to participate if they could provide the intervention. We see the staff experience and skills as an integral part of this package.

3. Will the analysis adjust for staff within centre and centre overall? The authors mention that the lack of blinding and the fact that since the 'same surgeons' treat both groups might 'insinuate a learning bias' but it isn't clear whether either an overall staff and/or centre effect will be included, nor whether a sensitivity
analysis exploring this possible contamination / learning effects will be undertaken?
We have decided to adjust for trial-site, but not for staff within centre. This has been clarified on page 13.
Until date all the participating trial-sites are providing the intervention on mixed-ICU’s in their available IC beds or ICU beds. None of the trial-sites have a surgical intermediate care unit. This will be reported in the result publication.

4. The text states that the 'compliance with the trial protocol' measures are listed in Table 3 - and that the comparison is at 48 hours - but the column in the Table seems to indicate these measures are made at 2 and 14 days? It would be unusual to measure an important outcome at different times between the two randomised groups? How would you deal with the differential death rate, for example?
We only register measures regarding compliance with the trial protocol and patient care (level of treatment and monitoring) at staggered times. The outcome measures are registered from The Danish Civil Registration System and medical chart at day 30.
This has been clarified on page 10, 11 and 18.

5. On the primary outcome of 30 day mortality the protocol states 'Mortality data will be retrieved from the Danish Civil Registration System (CRS) ... by CTU at interim analysis and at day 30 after the last patient has been enrolled' - couple of points:

a. what is CTU? Clinical Trials Unit?
Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. This is a research centre which supervise investigator initiated randomised trials initiated in Denmark. Copenhagen Trial Unit has programmed the telephone-based randomisation system and the trial database which is situated and managed at CTU by an independent data coordinator. This has been clarified on page 11, 12 and 24.

b. How complete and accurate is the DRS?
The Danish Civil Registration System is the National registration of Danish residents established for administrative purpose by the Danish government. It is generally accepted that the information is of very high quality. 1) The information is continuously recorded by the government which corrects errors when encountered; 2) ongoing validation is performed; 3) when established in 1968 all residents received a civil registration number card including their own personal information so that personal errors could be corrected and 4) registration in the CRS is required by law and necessary to get tax-financed health-care and other benefits. All new residents born after 1968 are registered at birth. Vital status is updated continuously and records whether the person is alive and resident in Denmark, emigrated or dead [2].

c. Wouldn't there be a lag in getting any death registered on the system?
The Danish Civil Registration System is an integrated part of the authority’s electronic case management system through the unique personal-identification number. Therefore there is no administrative lag in the registration.

d. Why all cause mortality and not an appropriate cause specific death specification - would the intervention be expected to influence all deaths
regardless of cause?
It is almost impossible to establish a unique cause of death in this patient group. Cause of death will almost always be multifactorial.

e. Why 30 days, and not say in-hospital (shorter) or 6-12 months (longer)?
We chose 30-day mortality over in-hospital mortality because reliable data can be retrieved from the CRS and thereby all participants have an equal follow-up time. Furthermore, short-term mortality has primarily been reported in previous research. We agree that long-term mortality is just as relevant, which is why we report it as the most important secondary outcome. The cause of death register in DK on the other hand is not reliable due to the very heterogeneous registration by physicians, and because the determination of the cause of death is highly subjective, prone to reflect the attending physicians belief rather than a thorough postmortem examination.

6. Not sure I understood the rationale behind the DMC stopping rules - specifically it seems to treat benefit and harm symmetrically - but if there is evidence of harm at P<0.001 at 200 patients, is it really acceptable to go on to recruit another 100 patients to have another look at n=300?
Firstly, as the primary outcome measure, mortality, is used as the criteria for eventual stopping there is no reason not to use a symmetric stopping criterion. Despite which of the interventions was superior it would be reasonable to stop for harm which would be to stop the intervention showing harm. Secondly, due to time lag of the interim-analysis results we expected nearly 100 patients to be recruited during the period of getting data from the CPR register in DK including the DSMC doing the analysis and reporting their recommendation for continuing or stopping the trial. The rationale behind the interim-analysis is that we wanted a independent DMC to evaluate the data halfway during the trial, but stopping after 200 participants if analysis of patients randomised during the interim-analysis period would reverse the result or make it less reliable seems inappropriate as it would possibly lead to contradictory results between the final analysis and the interim-analysis

7. Not clear why the authors are conducting both logistic and Cox models on the primary outcome?
The primary outcome measure is all-cause 30-day mortality. This will be analysed with unadjusted univariate logistic regression. Furthermore a multivariate logistic regression analysis will be made adjusting for stratification variables: trial-site, APACHE II score (10–14 or higher than 15), and perforated vis cera (yes versus no); and design variables: age, ASA score (1–2 or higher than 3), Cancer, and nature of surgery (+/- re-operation) [3]. The secondary outcome measures: all-cause mortality within the total observation time, is a time to event outcome. This will be analysed with an unadjusted Cox-regression analysis and a Cox-regression analysis adjusted for the above mentioned stratification variables and design variables.

8. What is the current status of recruitment?
The trial was terminated on the 30th of November 2012 with 290 participants enrolled in the trial. The Datamonitor Committee found a very low overall event rate of the primary outcome at the first interim-analysis as compared to the pre-trial estimated. This precluding any possibility to detect or reject the anticipated relative risk reduction of 34% as used in the sample size estimation.

Best regards
On behalf of the authors,

Morten Vester-Andersen, MD
Herlev University Hospital
Dept. of Anaesthesiology and Intensive Care Medicine
Denmark

Reference List

