PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The DIVERT-CARE (Collaboration Action Research & Evaluation) Trial Protocol: A Multi-Provincial Pragmatic Cluster Randomized Trial of Cardio-Respiratory Management in Home Care
AUTHORS	Costa, Andrew P; Schumacher, Connie; Jones, Aaron; Dash, Darly; Campbell, Graham; Junek, Mats; Agarwal, Gina; Bell, Chaim M; Boscart, Veronique; Bronskill, Susan E; Feeny, David; Hébert, Paul C; Heckman, George; Hirdes, John; Lee, Linda; McKelvie, Robert S; Mitchell, Lori; Sinha, Samir; Davis, Joy; Priddle, Tammy; Rose, Joanne; Gillan, Roslyn; Mills, Deborah; Haughton, Dilys

VERSION 1 – REVIEW

REVIEWER	dr. T.N. Bonten Leiden University Medical Center, Public Health & Primary Care
REVIEW RETURNED	15-Apr-2019

GENERAL COMMENTS	- abstract: primary outcome not well described, please change it corresponding to the description in table 1 No other comments, well described and clear study protocol

REVIEWER	George Taler, MD Professor Clinical Medicine Geriatrics and Long Term Care Georgetown University School of Medicine 3900 Reservior Road, NW Washington, DC 20007 United States
REVIEW RETURNED	06-May-2019

GENERAL COMMENTS	Thank you for including both non-hospitalized and post-hospitalized subjects, but include analyses that separate the 2 populations. This in an important distinction in targeting future investigations. Please include questions of the providers concerning the appropriateness of 1) allowing patients to adjust their own medications under physician guidance and 2) the use of in-home monitoring technologies to improve detection or corroborate clinical suspicion of early exacerbation of the chronic disease state. Finally, in planning for the future, what diagnostic capabilities and treatment modalities would the providers recommend if ambulance personnel were to be able to evaluate and treat patients at home under telehealth consultation with emergency or primary care physicians.

REVIEWER	Tamra Keeney Brown University, United States of America
REVIEW RETURNED	20-May-2019

GENERAL COMMENTS	The authors have presented a well written protocol detailing their study, which is a pragmatic trial of a home-care cardio-respiratory management model vs. usual care. Overall, the protocol is well-written, but there are a few points that require clarification: 1. Page 4, Lines 15-16: This last bullet point states that the care model is designed for longitudinal care environments rather than short-term PAC settings. Although this is a valid point, the sentence is a bit confusing as the authors do not clearly discuss this in the introduction. The authors need to more explicitly argue the superiority of their decision to focus on longitudinal care environments rather than short-term PAC settings. I think the authors try to support this on page 5, lines 50-55, but it is ambiguous as written. 2. The components of the intervention model are well described, but the protocol would benefit from a few sentences that clearly compare and contrast the intervention vs. usual care. Currently, there is little information about the usual care provided for these patients or why the intervention model is an improvement over usual care. 3. Table 2 Routine Measurement: For health-related quality of life, the only assessment indicated is at 4 months. This could be a typo, but how would you assess change in HRQOL without baseline measurement? Additionally, it may be helpful to provide information regarding the sensitivity of measures of HRQOL and PAM-13 in the study. If these measures have not been shown to be sensitive to change over time, it would be difficult to ascertain any positive or negative change in these domains over the course of the study. 4. Figure 2: Further discussion is needed regarding selection of sub-groups for intervention in this study. Why are the the authors focused on sub-groups 9,10,14, and 15? Is there an empirically based reason for doing so? Why are individuals with cardio-respiratory symptoms with 2 or more episodes of hospital or ED use in the past 90 days excluded from this study, but individuals with 1 episode are included?

REVIEWER	Samuel J. Stratton, MD, MPH University of California, Los Angeles Fielding School of Public Health USA
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	This research is very well designed and organized. The research question is important to answer and the study will provide clarity on the topic. Writing style is very good. Strengths of the study are well described and include use of a validated prognostic case-finding method to assign baseline risks for subjects. Cluster randomization of caseloads (probability sampling) which allows for quantitative statistical analysis and generalizing of results. The research follows CONSORT

	Guidelines and uses administrative data for outcome, which helps limit potential bias. Suggestions are provided below to add clarity to the manuscript: 1. Important for cluster analysis sampling is that the research target population be relatively homogeneous. While selected sample sites are assessed for affect of results by nested random effects analysis, it would be helpful to note when describing the sites, why they (Ontario, Newfoundland, and British Columbia) were selected and if they are estimated to be homogeneous representatives of the target study population. 2. A detailed discussion of the challenges and known limitations of the research was not noted. One limitation to note is that while the overall study is randomized, there is a non-probability sampling effect present in that care service providers selected the case loads for the study inclusion (purposeful sampling technique). 3. On page 12, lines 3-8: suggest that the Ethics Board (Committee) that waived need for individual informed consent be noted here. The Ethics Board is noted earlier and later in the manuscript, but it would help clarify comments regarding consent if also noted at this point. 4. On page 17, line 14: suggest stating the statistical test used for the calculation of p-value that is referred to for clarity. 5. Page 17: suggest providing a specific definition for "total care costs". Thank you for the opportunity to review this manuscript. I look forward to seeing the final results. The research is extremely well designed and the researchers are to be congratulated for excellent work.

REVIEWER	Mike Bradburn University of Sheffield, UK
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	My main review focus is the statistical aspects Randomisation: At present this protocol doesn't address allocation concealment. Please clarify how the randomisation is carried out ie how does a care home get randomised? Primary outcome i) The "difference in median days" appears in WHO registration summary table but not the analysis. Should this be amended to "hazard ratio..." or Is medians the metric by which the groups will be compared? If the latter I can see a few problems. 1) The sample size shows that less than half of patients attend ED in each group; the median is therefore not reached within 6 months. The median *among those who attend* is defined, but this is a false metric if it does not account for the potential difference in the proportion of attendees. 2) If the median difference is to be presented, describe how this and its confidence interval will be produced. A median can be

	derived via the model and a CI via bootstrap, but please say if this is the case including the number of repetitions. 3) Related to this, the trial is powered on a hazard ratio of 0.75 but not a difference in medians: if the latter is the metric of choice, the power may be compromised. As an example, consider two curves which initially diverge but later rejoin: the null hypothesis may be rejected for the hazard ratio but not the difference in medians and vice versa. For reasons 1+3 in particular I advise against using a median as the primary vehicle for quantifying the difference between arms. I realise this doesn't help In terms of what should be used though. The standard approach is the hazard ratio, though two counter-arguments are -A hazard ratio is not as interpretable. -If there is non-PH, then by definition there is no single HR which quantifies the difference between arms. If the first can be tolerated, the second objection can be addressed by considering an alternative model if (and only if) propotionality doesn't hold. In this case, two alternatives would be 1) parametric accelerated failure times, in which the coefficient is the ratio of the geometric means. In particular a log-normal model is interpretable as the ratio of the (extrapolated) medians. Its distributional assumptions may not be met by the data well, however; these would need testing. 2) flexible parametric models, also known as the Royston-Parmar method (https://doi.org/10.1002/sim.1203). The (restricted) mean differences are interpretable and particularly relevant to the economic analysis. ii) Again this has presumably been considered, but is there potential for dependent censoring? I'm not familiar with the context but if a patient is discharged, are they in a sense "recovered" and no longer in need of services? If so, consider augmenting the analyses with a binary "did the person need services, yes/no?" Secondary outcomes, A general recommendation is to include baseline score as covariate if change score is used: see, for example Kent et al (https://doi.org/10.1161/STROKEAHA.108.532051), van Breukelen (https://doi.org/10.1016/j.jclinepi.2006.02.007). I'm aware that it's also inadvisable to change a planned analysis, but please consider this if only as a supportive analysis There are three points which the SPIRIT checklist may not be met: Item 5d: Please clarify does this trial have a DMEC, TSC or other oversight committee? Items 11b-d & 20c: is uptake of/adherence to the DIVERT tool being assessed, and if so are compliance- based analyses (eg per-protocol or CACE) planned? Item 21b: I assume there are no interim analyses or formal stopping rules but please state.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: dr. T.N. Bonten

Institution and Country: Leiden University Medical Center, Public Health & Primary Care

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below

- abstract: primary outcome not well described, please change it corresponding to the description in table 1

No other comments, well described and clear study protocol

RESPONSE: Thank you for your review. We have enhanced the description of the primary outcome in the abstract to align with Table 1.

Reviewer: 2

Reviewer Name: George Taler, MD

Institution and Country: Professor Clinical Medicine Geriatrics and Long Term Care, Georgetown University School of Medicine, 3900 Reservior Road, NW, Washington, DC 20007, United States

Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

Thank you for including both non-hospitalized and post-hospitalized subjects, but include analyses that separate the 2 populations. This in an important distinction in targeting future investigations.

RESPONSE: Thank you for your review. Our trial is focused on the home care population. As we describe on page 5 (Introduction, 6th paragraph), the majority of home care patients are referred directly from the community with no hospital involvement, but can be frequently classified as 'post-acute' at any given time given their high rate of hospitalization. The distinction of 'post-hospitalized' in this group is highly sensitive to timeframe (30, 60, or 90 days, etc) and, therefore, somewhat tenuous. We could not power the study to examine it, but we will examine non-hospitalized and post-hospitalized subjects in a post-hoc subgroup analysis.

Please include questions of the providers concerning the appropriateness of 1) allowing patients to adjust their own medications under physician guidance and 2) the use of in-home monitoring

technologies to improve detection or corroborate clinical suspicion of early exacerbation of the chronic disease state.

RESPONSE: Our intervention includes a clinical pharmacist-led medication review for safety, efficacy, appropriate use, and delivery options. This component is delivered at the discretion of the local clinical pharmacist group according to their local practice standards. Home care patients do not commonly receive mediation reviews, so our intent was to test it as part of the overall model of care. We did not test specific methods of medication management nor understand the views of providers on specific methods. In-home monitoring technologies are not common nor standardized in home care. Our pragmatic approach did not introduce new technologies, but rather leveraged what was existing. A program evaluation and qualitative study will be conducted in parallel (see page 16th), and we anticipate that these themes may emerge.

Finally, in planning for the future, what diagnostic capabilities and treatment modalities would the providers recommend if ambulance personnel were to be able to evaluate and treat patients at home under telehealth consultation with emergency or primary care physicians.

RESPONSE: Though 'community paramedicine' models show great promise, it was not a formal component in our model of care. Though, again, a program evaluation and qualitative study will be conducted in parallel (see page 16th) and we anticipate that this theme may emerge.

Reviewer: 3

Reviewer Name: Tamra Keeney

Institution and Country: Brown University, United States of America

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

The authors have presented a well written protocol detailing their study, which is a pragmatic trial of a home-care cardio-respiratory management model vs. usual care. Overall, the protocol is well-written, but there are a few points that require clarification:

1. Page 4, Lines 15-16: This last bullet point states that the care model is designed for longitudinal care environments rather than short-term PAC settings. Although this is a valid point, the sentence is a bit confusing as the authors do not clearly discuss this in the introduction. The authors need to more explicitly argue the superiority of their decision to focus on longitudinal care environments rather than short-term PAC settings. I think the authors try to support this on page 5, lines 50-55, but it is ambiguous as written.

RESPONSE: Thank you for your review. We have revised this section to strictly include strengths and limitations of the design or methods (as requested by the editors). Rather than argue the superiority of our decision to focus on patients that are not specifically 'post-acute', or intention was to highlight that our population (home care clients) differs from other trials given that they are not specifically 'post-acute'. The majority of home care patients are referred directly from the community with no hospital involvement.

2. The components of the intervention model are well described, but the protocol would benefit from a few sentences that clearly compare and contrast the intervention vs. usual care. Currently, there is little information about the usual care provided for these patients or why the intervention model is an improvement over usual care.

RESPONSE: We have expanded our description of the usual care provided for these patients in the intervention section (see page 12).

3. Table 2 Routine Measurement: For health-related quality of life, the only assessment indicated is at 4 months. This could be a typo, but how would you assess change in HRQOL without baseline measurement? Additionally, it may be helpful to provide information regarding the sensitivity of measures of HRQOL and PAM-13 in the study. If these measures have not been shown to be sensitive to change over time, it would be difficult to ascertain any positive or negative change in these domains over the course of the study.

RESPONSE: Thank you for flagging this. Indeed, it was a typo. We have revised Table 2 and now describe the longitudinal construct validity and sensitivity of the HRQOL (MDS HIS/HUI2) and PAM-13 in the study.

4. Figure 2: Further discussion is needed regarding selection of sub-groups for intervention in this study. Why are the the authors focused on sub-groups 9,10,14, and 15? Is there an empirically based reason for doing so? Why are individuals with cardio-respiratory symptoms with 2 or more episodes of hospital or ED use in the past 90 days excluded from this study, but individuals with 1 episode are included?

RESPONSE: We expand on this in the Eligibility Criteria section. Specifically, the eligibility criteria for the trial will result in a population that is representative of non-palliative home care clients in Canada who have cardio-respiratory symptoms and conditions. It captures approximately 1/3 of all assessed home care clients. We excluded individuals with cardio-respiratory symptoms with 2 or more hospital or ED episodes in the past 90 days given that they were determined in a pilot study to have exceedingly complex psycho-social needs (such as housing) that we could not address. They account for less than 4% of home care clients

Reviewer: 4

Reviewer Name: Samuel J. Stratton, MD, MPH

Institution and Country: University of California, Los Angeles, Fielding School of Public Health, USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This research is very well designed and organized. The research question is important to answer and the study will provide clarity on the topic. Writing style is very good.

RESPONSE: Thank you for your review.

Strengths of the study are well described and include use of a validated prognostic case-finding method to assign baseline risks for subjects. Cluster randomization of caseloads (probability sampling) which allows for quantitative statistical analysis and generalizing of results. The research follows CONSORT Guidelines and uses administrative data for outcome, which helps limit potential bias.

Suggestions are provided below to add clarity to the manuscript:

1. Important for cluster analysis sampling is that the research target population be relatively homogeneous. While selected sample sites are assessed for affect of results by nested random effects analysis, it would be helpful to note when describing the sites, why they (Ontario, Newfoundland, and British Columbia) were selected and if they are estimated to be homogeneous representatives of the target study population.

RESPONSE: Thank you for your review. The three Canadian jurisdictions were selected from 5 potential jurisdictions that expressed interest based on their geographical (West, Central, and East) and political-cultural diversity. We now expand on this in the 'Study Population' section.

2. A detailed discussion of the challenges and known limitations of the research was not noted. One limitation to note is that while the overall study is randomized, there is a non-probability sampling effect present in that care service providers selected the case loads for the study inclusion (purposeful sampling technique).

RESPONSE: We have revised the protocol to include strengths and limitations of the design or methods (as requested by the editors).

3. On page 12, lines 3-8: suggest that the Ethics Board (Committee) that waived need for individual informed consent be noted here. The Ethics Board is noted earlier and later in the manuscript, but it would help clarify comments regarding consent if also noted at this point.

RESPONSE: In the section noted (Recruitment and Consent) we outline our justification for a waiver of individual informed consent based on the governing Canadian guidelines. On balance, we feel it would be unnecessary and also redundant to list the three review boards that granted the waiver (and provided approval). They are easily referenced in the under their appropriate headings.

4. On page 17, line 14: suggest stating the statistical test used for the calculation of p-value that is referred to for clarity.

RESPONSE: We list the hazard ratio estimated using a multi-level proportional hazards model.

5. Page 17: suggest providing a specific definition for "total care costs".

RESPONSE: We have now defined total care cost (i.e., direct costs to the home care provider) and have also included our costing approach.

Thank you for the opportunity to review this manuscript. I look forward to seeing the final results. The research is extremely well designed and the researchers are to be congratulated for excellent work.

Reviewer: 5

Reviewer Name: Mike Bradburn

Institution and Country: University of Sheffield, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

My main review focus is the statistical aspects

Randomisation:

At present this protocol doesn't address allocation concealment. Please clarify how the randomisation is carried out ie how does a care home get randomised?

RESPONSE: Thank you for your review. This is a cluster-randomized trial in which the unit of randomization is the home care caseload. Within each sub region of each site, caseloads were randomized to intervention or control at a 1:2 ratio using a blocked allocation sequence with a block size of 3 (see 'Allocation'). Due to the nature of the intervention, it is not possible to conceal the treatment assignment from the care coordinators who deliver the intervention or the patients who receive the invention. However, treatment assignment is concealed from outcome measured as the primary outcome is extracted from administrative hospital records. We have included this in the strengths and limitations section.

Primary outcome

i) The "difference in median days" appears in WHO registration summary table but not the analysis. Should this be amended to "hazard ratio..." or Is medians the metric by which the groups will be compared? If the latter I can see a few problems.

1) The sample size shows that less than half of patients attend ED in each group; the median is therefore not reached within 6 months. The median *among those who attend* is defined, but this is a false metric if it does not account for the potential difference in the proportion of attendees.

2) If the median difference is to be presented, describe how this and its confidence interval will be produced. A median can be derived via the model and a CI via bootstrap, but please say if this is the case including the number of repetitions.

3) Related to this, the trial is powered on a hazard ratio of 0.75 but not a difference in medians: if the latter is the metric of choice, the power may be compromised. As an example, consider two curves which initially diverge but later rejoin: the null hypothesis may be rejected for the hazard ratio but not the difference in medians and vice versa.

For reasons 1+3 in particular I advise against using a median as the primary vehicle for quantifying the difference between arms.

I realise this doesn't help In terms of what should be used though. The standard approach is the hazard ratio, though two counter-arguments are

-A hazard ratio is not as interpretable.

-If there is non-PH, then by definition there is no single HR which quantifies the difference between arms.

If the first can be tolerated, the second objection can be addressed by considering an alternative model if (and only if) propotionality doesn't hold. In this case, two alternatives would be

1) parametric accelerated failure times, in which the coefficient is the ratio of the geometric means. In particular a log-normal model is interpretable as the ratio of the (extrapolated) medians. Its distributional assumptions may not be met by the data well, however; these would need testing.

2) flexible parametric models, also known as the Royston-Parmar method (https://doi.org/10.1002/sim.1203). The (restricted) mean differences are interpretable and particularly relevant to the economic analysis.

ii) Again this has presumably been considered, but is there potential for dependent censoring? I'm not familiar with the context but if a patient is discharged, are they in a sense "recovered" and no longer in need of services? If so, consider augmenting the analyses with a binary "did the person need services, yes/no?"

RESPONSE: Our metric for comparing the treatment arms on the primary outcome is the hazard ratio. The reference to "difference in median days" is from an older version of the protocol. We will remedy this in the registration. As the protocol indicates, we will examine the proportionality assumption of the cox model and incorporate time-dependent effects as is appropriate. On the question of informative censoring, a patient may be discharged for a number of many reasons: they may have recovered and no longer needed services, they may have had no change in health status but prefer to discontinue services, or they have may declined and moved to a setting where they have more support (i.e. a nursing home). We do not believe that we will encounter a meaningful degree of informative censoring.

Secondary outcomes,

A general recommendation is to include baseline score as covariate if change score is used: see, for example Kent et al (https://doi.org/10.1161/STROKEAHA.108.532051), van Breukelen (https://doi.org/10.1016/j.jclinepi.2006.02.007). I'm aware that it's also inadvisable to change a planned analysis, but please consider this if only as a supportive analysis

RESPONSE: Thank you for flagging this. Excluding the baseline score was a typo. We have incorporated it into our analysis plan.

There are three points which the SPIRIT checklist may not be met:

Item 5d: Please clarify does this trial have a DMEC, TSC or other oversight committee?

RESPONSE: No such committee was required and we have updated the protocol accordingly (see 'Harm' section).

Items 11b-d & 20c: is uptake of/adherence to the DIVERT tool being assessed, and if so are compliance- based analyses (eg per-protocol or CACE) planned?

RESPONSE: The uptake of each portion of the DIVERT intervention is being recorded and will be reported (see Statistical Analyses). However, as this is a pragmatic trial we are not planning any compliance-based analysis. This has been added to the same section.

Item 21b: I assume there are no interim analyses or formal stopping rules but please state.

RESPONSE: There are no formal stopping rules or interim analyses and we have updated the protocol accordingly (see 'Harm' section).

VERSION 2 – REVIEW

REVIEWER	Tamra Keeney, DPT, PhD Brown University School of Public Health, USA
REVIEW RETURNED	02-Oct-2019

GENERAL COMMENTS	The authors have done a thorough job of responding to reviewer comments. I look forward to seeing the results of this investigation.

REVIEWER	Sam J. Stratton, MD, MPH University of California, Los Angeles Los Angeles, CA USA
REVIEW RETURNED	24-Sep-2019

GENERAL COMMENTS	Thank you for the opportunity to review this revision of the original manuscript. The Authors have addressed the prior concerns brought forward by reviewers. The manuscript reads well and is well organized. Statistical methods and format are well described and appropriate to the data generated by the research.

REVIEWER	Mike Bradburn University of Sheffield
REVIEW RETURNED	20-Sep-2019

GENERAL COMMENTS	I had one remaining comment, which was to clarify the previous question regarding allocation concealment. I realise this study cannot be blinded: the comment referred to how allocation was withheld. More specifically, allocation concealment would mean home care sites do not know what allocation they will receive when agreeing to enter the trial. If the randomisation list was prepared centrally and not revealed to prospective sites then this strengthens the trial: please state if this was the case. Other than this the authors have addressed my previous (and mostly minor) questions.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name

Tamra Keeney, DPT, PhD

Institution and Country

Brown University School of Public Health, USA

Please state any competing interests or state 'None declared':
None declared.
Please leave your comments for the authors below
The authors have done a thorough job of responding to reviewer comments. I look forward to seeing the results of this investigation.

RESPONSE: Thank you

Reviewer: 4
Reviewer Name

Sam J. Stratton, MD, MPH

Institution and Country

University of California, Los Angeles
Los Angeles, CA
USA

Please state any competing interests or state 'None declared':
None
Please leave your comments for the authors below
Thank you for the opportunity to review this revision of the original manuscript. The Authors have

addressed the prior concerns brought forward by reviewers. The manuscript reads well and is well organized. Statistical methods and format are well described and appropriate to the data generated by the research.

RESPONSE: Thank you

Reviewer: 5
Reviewer Name

Mike Bradburn

Institution and Country

University of Sheffield

Please state any competing interests or state ‘None declared’:
None declared
Please leave your comments for the authors below
I had one remaining comment, which was to clarify the previous question regarding allocation concealment. I realise this study cannot be blinded: the comment referred to how allocation was withheld. More specifically, allocation concealment would mean home care sites do not know what allocation they will receive when agreeing to enter the trial. If the randomisation list was prepared centrally and not revealed to prospective sites then this strengthens the trial: please state if this was the case.

Other than this the authors have addressed my previous (and mostly minor) questions.

RESPONSE: Thank you for that clarification. Caseload randomization was designed and completed centrally and not revealed to prospective sites until after site caseloads were enrolled. We have included this in the “Allocation” section.