Aldosterone antagonists for people with chronic kidney disease requiring dialysis (Protocol)

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T A B L E   O F   C O N T E N T S

Aldosterone antagonists for people with chronic kidney disease requiring dialysis

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A B S T R A C T

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

This review aims to assess the benefits and harms of aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), in comparison to placebo or no intervention or standard care in people with ESKD requiring haemodialysis or peritoneal dialysis.

B A C K G R O U N D

Description of the condition

Over 2.6 million people were estimated to have end-stage kidney disease (ESKD) requiring dialysis worldwide in 2010, with this number expected to more than double by 2030 (Liyanage 2015). Accordingly, the global health burden arising from people with ESKD needing renal replacement therapy (RRT) has been rapidly increasing in recent years.

People with ESKD requiring dialysis have especially high risk of cardiovascular death and morbidity (Foley 1998; USRDS 2017a). Hypertension, heart failure, and left ventricular hypertrophy are particularly common among people with chronic kidney disease (CKD) undergoing dialysis. The recent epidemiological data based on the US Renal Data System (USRDS) (USRDS 2017a) revealed that the prevalence of any cardiovascular disease was more common in people receiving haemodialysis (69.8%) than those receiving peritoneal dialysis (56.6%). The USRDS also showed that 48% of deaths in this population weree due to cardiovascular events including arrhythmia/cardiac arrest, acute myocardial infarction and atherosclerotic heart disease, and congestive heart failure (USRDS 2017b). These features greatly contribute to their death and morbidity (Foley 1995; Harnett 1995; Salem 1995; USRDS 2017a; USRDS 2017b).

In healthy people, aldosterone is a mineral corticosteroid hormone produced by the adrenal gland, which regulates water and salt balance in the body by stimulating absorption of sodium and excretion of potassium by the kidneys. However, excess aldosterone induces cardiac fibrosis and vascular damage, and consequently

can result in heart failure and kidney injury. In people requiring dialysis, serum aldosterone concentration can be elevated and independently associated with left ventricular hypertrophy (Sato 1999; Steigerwalt 2007). Therefore, it has been postulated that aldosterone antagonists would be a promising therapeutic option for people on dialysis with cardiovascular disease. Moreover, the residual kidney function could result in both crucial benefits and possible harm because potassium excretion by the kidneys needs tubular flow of urine.

Description of the intervention

Aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), are oral antihypertensive pharmaceutical agents that block the effect of aldosterone at the mineralocorticoid receptors in myocardium, endothelium, and vascular smooth muscles. Administration of aldosterone antagonists may raise serum potassium especially in people without residual kidney function, and the major concern of its use in people requiring dialysis is life-threatening hyperkalaemia. However, several investigations have suggested that aldosterone antagonists can be safely given to people with ESKD on dialysis (Gross 2005; Saudan 2003; Walsh 2015).

How the intervention might work

Previous studies have shown protective effects of aldosterone antagonists on death and morbidity in people with cardiovascular disease (Pitt 1999; Pitt 2003). Addition of aldosterone antagonists to renin-angiotensin system (RAS) inhibitors may address problems with the 'aldosterone escape phenomenon' (Staessen 1981) - a phenomenon which describes the incomplete suppression of serum aldosterone levels with RAS inhibitors alone - and could further improve clinical outcomes of people with heart failure (Yancy 2013).

Recent randomised controlled trials (RCTs) involving people with ESKD who are on dialysis have evaluated the role of both spironolactone and eplerenone in death, morbidity, blood pressure, serum potassium, and on echocardiographic findings including left ventricular mass and ejection fraction (Feniman-De-Stefano 2015; Gross 2005; Ito 2014; Lin 2016; Matsumoto 2014; Ni 2014; Saudan 2003; Taheri 2009; Taheri 2012; Vukusich 2010; Walsh 2015; Yongsiri 2015). It has been reported that spironolactone may lower blood pressure without also resulting in hyperkalaemia in people receiving haemodialysis (Gross 2005; Ni 2014). On the other, one RCT found that eplerenone increased serum potassium levels slightly with no effect on blood pressure (Walsh 2015). Other RCTs have found that spironolactone prevented progression of left ventricular hypertrophy irrespective of blood pressure control in people on peritoneal dialysis (Ito 2014) and haemodialysis (Feniman-De-Stefano 2015). Furthermore, Matsumoto 2014 indicated the effects of spironolactone on cardiovascular and cere-

brovascular morbidity and death in people receiving haemodialysis in an RCT with a 3-year follow-up. A more recent RCT has also shown that spironolactone reduced the risk of cardiovascular death and morbidity and improved cardiovascular-related indexes in people requiring dialysis without heart failure (Lin 2016).

Why it is important to do this review

Previous systematic reviews have shown that aldosterone antagonists reduces proteinuria and blood pressure but increases hyperkalaemia in people with CKD who are not receiving dialysis, and that it improves survival of patients with chronic heart failure in combination with CKD (Bolignano 2014). Recently, Quach 2016 published a non-Cochrane systematic review that involved a meta-analysis of nine studies (829 patients) testing the safety and efficacy of aldosterone antagonists in people receiving dialysis. This investigation report that patients undergoing dialysis who were treated with aldosterone antagonists had a reduced relative risk (RR) for cardiovascular and all-cause death compared with control patients (RR 0.34, 95% CI 0.15 to 0.75 and RR 0.40, 95% CI 0.23 to 0.69, respectively). The authors also indicated that aldosterone antagonists tended to cause hyperkalaemia (RR 3.05, 95%CI 1.21 to 7.70). However, there is still some uncertainty about both the benefits and harms of aldosterone antagonists for people with CKD requiring dialysis. Indeed, since completion of the review by Quach 2016, a new, large RCT (n = 258) has been published, which assesses the long-term (two years) effects and adverse events in this population (Lin 2016). Furthermore, the meta-analysis by Quach 2016 only evaluated cardiovascular and all-cause death, hyperkalaemia, blood pressure including hypotension events, and gynaecomastia. The other important surrogate outcomes such as cardiovascular-related indexes, including left ventricular mass based on echocardiographic findings (which would consequently affect the prognosis of the people requiring dialysis) have never been systematically evaluated. There are also several ongoing trials including ACHIEVE (ClinicalTrials.gov Identifier: NCT03020303), SpinD (NCT02285920) and ALCHEMIST (NCT01848639) which will provide addition data on this important issue. Finally, the financial burden of cardiovascular death and morbidity among dialysis population is huge. Aldosterone antagonists may provide an important low-cost treatment option if they are found to be clinically effective.

O B J E C T I V E S

This review aims to assess the benefits and harms of aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), in comparison to placebo or no intervention or standard care in people with ESKD requiring haemodialysis or peritoneal dialysis.

M E T H O D S

Criteria for considering studies for this review

Types of studies

All parallel-group RCTs and quasi-RCTs (where group allocation is by a method that is not truly random, such as alternation, assignment based on alternate medical records, date of birth, case record number, or other predictable methods) looking at aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), use in comparison to placebo or no intervention or standard care in people with ESKD requiring haemodialysis or peritoneal dialysis.

Types of participants

Inclusion criteria

People with ESKD (CKD stage 5D) defined by Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines (Levey 2011), who are being treated with RRT including haemodialysis or peritoneal dialysis.

Exclusion criteria

We will exclude studies involving people with ESKD who have received a kidney transplant.

Types of interventions

We will include studies comparing aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), to placebo, no intervention, standard care, or head-to head studies.

Types of outcome measures

The outcomes selected include the relevant SONG core outcome sets as specified by the Standardised Outcomes in Nephrology initiative (SONG 2017). The outcome measures in studies will not form part of the inclusion/exclusion criteria.

Primary outcomes

1. Death (all-cause and cardiovascular)*
2. Cardiovascular* and cerebrovascular morbidity including but not limited to myocardial infarction, stroke, congestive heart failure.
3. Adverse events (hyperkalaemia defined as serum potassium > 5.0, 6.5, 6.8 mEq/L)

Secondary outcomes

1. Left ventricular mass based on echocardiographic findings
2. Ejection fraction based on echocardiographic findings
3. Residual kidney function
4. Blood pressure
5. Serum potassium
6. Vascular access failure*
7. Fatigue score*
8. Gynaecomastia
9. Peritoneal function (only in people undergoing peritoneal dialysis)

*The SONG core outcomes.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Register of Studies through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of hand searched journals, conference proceedings and current awareness alerts, are available in the *Specialised Register* section of information about Cochrane Kidney and Transplant. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

We will use the search strategy described above to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable. However studies and reviews that might include relevant data or information on trials will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria. Any disagreement will be resolved through consensus with two authors or by a third author if consensus will not be reached.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Depending on available resources, we will translate studies reported in non-English language journals before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  ○ Participants and personnel (performance bias)
  ○ Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

We will express dichotomous outcomes (e.g. death, cardiovascular and cerebrovascular morbidity, hyperkalaemia, vascular access failure) as RR. We will report continuous outcome data (e.g. left ventricular mass and ejection fraction based on echocardiographic findings, residual kidney function, blood pressure, serum potassium, fatigue score) as mean difference (MD) if the same measurement scales have been used, or as standardised mean differences (SMD) if different scales have been used. We will report 95% confidence intervals (95% CI) for all outcomes.

Unit of analysis issues

We do not consider unit of analysis issues because we will use data from parallel RCTs only.

Dealing with missing data

We will request further information from the original authors of included studies if this is required (e.g. emailing corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I² statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I² values will be as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity

The importance of the observed value of I² depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi² test, or a confidence interval for I²) (Higgins 2011).

Assessment of reporting biases

If possible, we will use funnel plots to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

We will pool data using the random-effects model but will examine the influence of the fixed-effect model to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analysis to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). We will test the following subgroups.

- Dialysis modality: haemodialysis or peritoneal dialysis.
- Residual kidney function: with or without residual kidney function.
- Aetiology of initial kidney disease: diabetic kidney disease or the others.
- Concomitant use of RAS inhibitors or not.

Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size: repeating the analysis excluding unpublished studies and excluding the studies at high risk of bias for allocation concealment and incomplete outcome data. We will also conduct separate analyses for hyperkalaemia as an adverse event using various threshold values for serum potassium (> 5.0, 6.5, 6.8 mEq/L).

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables for comparing aldosterone antagonists, both non-selective (spironolactone) and selective (eplerenone), to placebo, no intervention, or standard care. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

1. Death (all-cause and cardiovascular)*
2. Cardiovascular and cerebrovascular morbidity including but not limited to myocardial infarction, stroke, and congestive heart failure.
3. Adverse events (hyperkalaemia defined as serum potassium > 5.0, 6.5, 6.8 mEq/L)
4. Left ventricular mass based on echocardiographic findings
5. Ejection fraction based on echocardiographic findings
6. Residual kidney function
7. Serum potassium

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Renal Replacement Therapy] this term only
	2. MeSH descriptor: [Renal Dialysis] this term only
	3. MeSH descriptor: [Peritoneal Dialysis] explode all trees
	4. MeSH descriptor: [Hemodiafiltration] this term only
	5. MeSH descriptor: [Hemodialysis, Home] this term only
	6. (hemodialysis or haemodialysis):ti,ab,kw (Word variations have been searched)
	7. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched)

	8. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched)
	9. "end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal":ti,ab,kw (Word variations have been searched)
	10. ESKD or ESKF or ESRD or ESRF:ti,ab,kw (Word variations have been searched)
	11. CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched)
	12. {or #1-#11}
	13. MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
	14. spironolactone:ti,ab,kw (Word variations have been searched)
	15. eplerenone:ti,ab,kw (Word variations have been searched)
	16. canrenone:ti,ab,kw (Word variations have been searched)
	17. {or #13-#16}
	18. {and #12, #17}
MEDLINE	1. Renal Replacement Therapy/
	2. Renal Dialysis/
	3. exp Peritoneal Dialysis/
	4. (CAPD or CCPD or APD).tw.
	5. Hemodiafiltration/
	6. Hemodialysis, home/
	7. dialysis.tw.
	8. (hemodialysis or haemodialysis).tw.
	9. (hemofiltration or haemofiltration).tw.
	10. (hemodiafiltration or haemodiafiltration).tw.
	11. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw.
	12. (ESKD or ESKF or ESRD or ESRF).tw.
	13. or/1-12
	14. exp Mineralocorticoid Receptor Antagonists/
	15. Diuretics, Potassium Sparing/
	16. spironolactone.tw.
	17. eplerenone.tw.
	18. canrenone.tw.
	19. or/14-17
	20. and/13,19
EMBASE	1. Kidney Failure/
	2. renal replacement therapy/
	3. end stage renal disease/
	4. renal replacement therapy-dependent renal disease/
	5. extended daily dialysis/
	6. hemodiafiltration/
	7. hemofiltration/
	8. exp hemodialysis/
	9. exp peritoneal dialysis/
	10. (hemodialysis or haemodialysis).tw.
	11. (hemofiltration or haemofiltration).tw.
	12. (hemodiafiltration or haemodiafiltration).tw.
	13. dialysis.tw.
	14. peritoneal dialysis.tw.
	15. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.

16. (CAPD or CCPD or APD).tw.	
17. (ESRF or ESKF or ESRD or ESKD).tw.	
18. or/1-17	
19. exp mineralocorticoid antagonist/	
20. spironolactone.tw.	
21. canrenone.tw.	
22. eplerenone.tw.	
23. or/19-22	
24. and/18,23	

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available

Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically rel-

	evant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: TH, EO, WL

2. Study selection: TH, HNishiwaki

3. Extract data from studies: TH, HNishiwaki

4. Enter data into RevMan: TH

5. Carry out the analysis: TH, HNishiwaki, EO, WL, HNoma

6. Interpret the analysis: TH, HNishiwaki

7. Draft the final review: TH, HNishiwaki, EO, WL, HNoma

8. Disagreement resolution: TH, HNishiwaki, EO

9. Update the review: TH, HNishiwaki, EO

DECLARATIONS OF INTEREST

- TH: has consultancy agreement with Kyowa Hakko Kirin and has received speaker honoraria from Kyowa Hakko Kirin, and Astellas for activities unrelated to this review

- HNishiwaki: none known

- EO: none known

- WL: none known

- HNoma: none known