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Yoga for women diagnosed with breast cancer (Protocol)

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[Intervention Protocol]

Yoga for women diagnosed with breast cancer

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of yoga on health-related quality of life, mental health, and cancer-related symptoms in women diagnosed with breast cancer who are on active treatment or have completed treatment.

BACKGROUND

Description of the condition

With more than 1.3 million new cases each year, breast cancer is the most frequently diagnosed cancer in women worldwide (Ferlay 2010). While still more than 450,000 women will die from breast cancer each year (Ferlay 2010), advances in cancer prevention, diagnosis, and treatment have led to a continuous increase in survival rates (Berry 2005). During breast cancer treatment, about one third of women experience substantial psychological distress, mainly depression and anxiety (Stafford 2013), that does not significantly decrease over time (Hopwood 2010). These psychological impairments can aggravate symptom burden and seriously affect health-related quality of life (Andrykowski 2008). Cancer-related fatigue is another important symptom that interferes with usual functioning (Patrick 2003). Up to 90% of women with breast cancer experience fatigue during chemotherapy (Hartvig 2006; Schmidt 2012), which may endure for several years (Bower 2006; Garabeli Cavalli Kluthcovsky 2012). Sleep disturbance is also highly prevalent in women with breast cancer, prior to surgery, during subsequent chemotherapy (Van Onselen 2012), and during anti-hormonal treatment (Desai 2013).

Description of the intervention

Yoga has its roots in Indian philosophy and has been a part of traditional Indian spiritual practice for about 4000 years (Feuerstein 1998). Being a complex intervention, yoga comprises advice for an ethical lifestyle, spiritual practice, physical activity, breathing exercises, and meditation (De Michaelis 2005; Feuerstein 1998). While yoga originally evolved as a spiritual practice, it has become a popular means to promote physical and mental well-being (De Michaelis 2005; Feuerstein 1998). In North America and Europe, yoga is most often associated with physical postures (asanas), breathing techniques (pranayama), and meditation (dyana) (De Michaelis 2005; Feuerstein 1998). Contrary to popular perceptions, meditation and breathing techniques are inherent parts of yoga practice. Different yoga forms have emerged that put varying focus on physical and mental practices (Feuerstein 1998). While

most yoga forms practised in North America and Europe mainly focus on postures, many yoga traditions only include meditation (Shannahoff-Khalsa 2005) or breathing techniques (Brown 2005) without specific physical components. An estimated 15 million American adults report having practised yoga at least once in their lifetime, almost half of these adults use yoga explicitly for coping with disease or promoting health (Saper 2004).

How the intervention might work

It is now widely accepted that therapeutic exercise programs for women diagnosed with breast cancer who are on active treatment or have completed treatment can significantly improve physical functioning and quality of life, and mitigate fatigue (McNeely 2006; Visovsky 2006). In addition, exercise decreases the percentage of body fat, improves cardiopulmonary function (Kim 2009; McNeely 2006), and decreases mortality rates in women who have completed treatment for breast cancer (Ibrahim 2011). Physical exercise reduces the blood insulin level (Irwin 2009), strengthens the immune system, and promotes the catabolism of stress hormones and oestrogens (Neilson 2009). Furthermore, exercising together in a group of similarly affected women should enhance the individual's quality of life (Floyd 2009). While yoga involves physical activity, it differs from purely gymnastic exercise in that the practitioner focuses her mind on the postures with inner awareness and a meditative focus of mind (Büssing 2011; Cramer 2013). A proposed mechanism of how yoga could positively influence mental and physical health is a decrease of dysregulation in the hypothalamic-pituitary-adrenal axis; this is the stress response (Carroll 2012; Streeter 2012). Yoga can decrease subjective stress in healthy adults (Chong 2011) and reduce levels of plasma cortisol in individuals with cancer (Banasik 2011; Vadiraja 2009) and psychiatric patients (Devi 1986; Vedamurthachar 2006). Imaging studies have shown that yoga can increase endogenous dopamine release in the ventral striatum (Kjaer 2002) and thalamic gamma-aminobutyric acid (GABA) levels (Streeter 2010). Both dopamine (Syvälahti 1994) and GABA (Kalueff 2007) play a major role in the pathophysiology of psychological distress. It has been hypothesised that by increasing GABA activity, yoga can reduce allostatic load in stress response systems such that optimal homeostasis is restored (Streeter 2012).

Why it is important to do this review

Many women who are currently undergoing treatment or have completed treatment for breast cancer use complementary medicine (NIH 2012) to manage the effects of the disease (Fouladbakhsh 2010), and yoga is among the most commonly used complementary therapies for breast cancer-related impairments (Fouladbakhsh 2010). Systematic reviews and meta-analyses have shown that yoga can improve health-related quality of life in cancer patients (Buffart 2012; Culos-Reed 2012; Lin 2011; Smith 2009). However, as individuals with different types of cancer are heterogeneous in terms of socio-demographic factors, symptoms, treatment and side effects, meta-analyses should focus on homogenous cancer groups. It is obvious from previous reviews that the vast majority of studies on yoga for cancer have involved women on active treatment or who have completed treatment for breast cancer. Four systematic reviews so far have explicitly focused on women undergoing treatment or who have completed treatment for breast cancer (Cramer 2012; Harder 2012; Levine 2012; Zhang 2012) and only two of these included meta-analyses (Cramer 2012; Zhang 2012). Based on six randomised trials that compared yoga to no treatment, Zhang 2012 found significant effects favouring yoga on health-related quality of life but not on psychological outcomes. In contrast, Cramer 2012 found positive effects of yoga compared to no treatment or active control interventions on health-related quality of life, depression, and anxiety. Besides health-related quality of life and mental health, only one prior review assessed physical cancer-related symptoms and this review did not include a meta-analysis (Harder 2012). Evidence for effects on fatigue was inconclusive, with three out of seven included trials reporting positive effects of yoga.

Mainly based on anecdotal evidence, the safety of yoga has been questioned in the lay press (Broad 2012). As this seems to have led to a general uncertainty among yoga practitioners and those interested in starting practice, it seems important to systematically assess the safety of yoga. However, no prior review on yoga for women with breast cancer has quantitatively analysed safety data. Therefore, a comprehensive review of both the efficacy (in terms of health-related quality of life, physical and mental health) and safety of yoga for women undergoing active treatment or who have completed treatment for breast cancer seems warranted.

OBJECTIVES

To assess the effects of yoga on health-related quality of life, mental health, and cancer-related symptoms in women diagnosed with breast cancer who are on active treatment or have completed treatment.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) assessing the effects of yoga in women with breast cancer undergoing treatment or who

have completed treatment, or both. Both full text and abstract publications will be eligible if sufficient information is available on study design, characteristics of participants, interventions, and outcomes.

Types of participants

Women with a histologically confirmed diagnosis of non-metastatic or metastatic breast carcinoma (Stage I - IV) as defined by the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system (Compton 2012).
Women diagnosed with breast cancer and who have completed treatment (that is, completed initial management of Stage I - IV breast cancer) will also be eligible.
No limits will be applied regarding age groups or settings.
Studies including participants with other cancer types will be excluded unless the outcomes for the breast cancer subgroup are reported separately.

Types of interventions

Any form of yoga will be eligible as the experimental intervention (for example Hatha yoga, Ashtanga yoga, Iyengar yoga, Integrated yoga therapy, Viniyoga, Bikram Yoga, Sivananda yoga, Kundalini yoga, Tibetan yoga, Yoga of Awareness, or any other yoga form). Studies that do not mention a specific form of yoga but simply describe their intervention as 'yoga' will also be eligible. Interventions should include at least one of the following: yoga postures, breath control, meditation, and lifestyle advice (based on yoga theory or traditional yoga practices).
Studies on multimodal interventions such as mindfulness-based stress reduction, mindfulness-based cognitive therapy, or the Mind Body Program for Cancer by the Benson-Henry Institute for Mind Body Medicine (that includes yoga amongst other therapies) will be excluded as the relative effects of yogic practices cannot be assessed separately in such programs.
Attention control, waiting list control, treatment as usual, no therapy, or any other active therapy will be eligible as the comparator. Breast cancer treatments such as chemotherapy, radiotherapy, or anti-hormonal therapy, and supportive care will be allowed as long as the co-interventions are intended to be comparable between groups.

Types of outcome measures

Primary outcomes

- Health-related quality of life, assessed by any validated generic or disease-specific self-report scale
- Depression, assessed by any validated self-report or clinician-rated scale
- Anxiety, assessed by any validated self-report or clinician-rated scale
- Fatigue, assessed by any validated self-report scale
- Sleep disturbances, assessed by any validated self-report scale

When there is more than one measure for an outcome, standard instruments will be preferred over novel instruments and multi-item instruments over single-item instruments.

Secondary outcomes

- Safety of the intervention, assessed as number of women with adverse effects and number of women with severe adverse events

Search methods for identification of studies

Electronic searches

We will search the following databases.
(a) Cochrane Breast Cancer Group (CBCG) Specialised Register. Details of search strategies used by the CBCG for the identification of studies and the procedures used to code references are outlined in the CBCG's module at www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html. Trials with the key words "breast cancer", "early breast cancer", "locally advanced breast cancer", "advanced breast cancer", "high risk", "yoga", and "alternative/complementary therapy" will be extracted and considered for inclusion in the review.
(b) MEDLINE (via PubMed). See Appendix 1.
(c) EMBASE (via EMBASE.com). See Appendix 2.
(d) World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials. See Appendix 3.
(e) Clinicaltrials.gov (http://clinicaltrials.gov/). See Appendix 4.
(f) IndMED (http://indmed.nic.in/indmed.html). See Appendix 5.
(g) CENTRAL (2013, Issue 3). See Appendix 6.

Searching other resources

(a) Bibliographic searching.
We will try to identify further studies from reference lists of identified relevant trials or reviews. A copy of the full article will be obtained for each reference reporting a potentially eligible trial. Where this is not possible, attempts will be made to contact authors for them to provide additional information.
(b) Grey literature searching.
Conference proceedings of the following congresses and annual meetings of societies will be searched for relevant abstracts:

- International Congress on Complementary Medicine Research (ICCMR);
- European Congress for Integrative Medicine (ECIM);
- American Society of Clinical Oncology (ASCO).

Data collection and analysis

Selection of studies

Titles and abstracts of studies identified during the literature search will be screened independently by two review authors (HC and RL). Potentially eligible articles will be read in full by two review authors (HC and RL) to determine whether or not they meet the eligibility criteria. Disagreements will be discussed with a third review author (PK) until consensus is reached. If necessary, additional information will be obtained from the study authors.
Excluded studies will be recorded in the 'Characteristics of excluded studies' table.
The study selection process will be documented in a PRISMA flow chart (Moher 2009).
No language restrictions will be applied. Studies in languages other than English, German, French, Russian, Chinese, Norwegian, Swedish, or Islandic will be professionally translated.

Data extraction and management

Two review authors (PK and SL) will independently extract and enter data from all included studies into the 'Characteristics of included studies' table in the Review Manager software (RevMan). Disagreements will be discussed with a third review author (HC) until consensus is reached. A third review author (HC) will check the extracted data.
The information collected will include the following.

- Methods: study design, methods of allocation, allocation concealment, blinding, dropout rates and reasons for dropping out.
- Participants: country of origin, setting, sample size, diagnosis, age, ethnicity.
- Intervention: type, program length, frequency, duration (for experimental and comparator interventions).
- Outcomes: type of outcomes, assessment instruments, assessment time point, and follow-up time point.

For studies with more than one publication, the first publication will be considered as the primary reference but data will be extracted from all of the publications.

Assessment of risk of bias in included studies

Two review authors (PK and SL) will independently assess risk of bias using Cochrane's risk of bias assessment tool (Higgins 2011). Risk of bias will be assessed for the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other sources of bias.

Each domain will be judged as either:

- 'low risk of bias' if the requirements are adequately fulfilled, as described in Higgins 2011;
- 'high risk of bias' if the requirements are not adequately fulfilled, as described in Higgins 2011;
- 'unclear risk of bias' if insufficient data for a judgement are provided.

Risk of bias will be incorporated in judging the quality of evidence for each outcome according to the GRADE recommendations (Guyatt 2008).

Measures of treatment effect

Primary outcomes will be classified as continuous outcomes and expressed as standardised mean differences (SMD) with 95% confidence intervals (CI) according to the *Cochrane Handbook for Systematic Reviews of Interventions*, chapter 7, section 7.7.3 (Higgins 2011). SMD will be calculated as the difference in means between groups divided by the pooled standard deviation using Hedges' correction. Where available, final values will be preferred over change scores. A positive SMD will be defined to indicate beneficial effects of the experimental intervention compared to the comparator intervention for quality of life, while a negative SMD will be defined to indicate beneficial effects for mental health and cancer-related symptoms. If necessary, scores will be inverted by subtracting the mean from zero (Higgins 2011).
Secondary outcomes will be classified as dichotomous outcomes and expressed as risk ratios (RR) with 95% CI. RR will be calculated by dividing the risk of an event in the experimental group (that is the number of participants with the respective outcome divided by the total number of participants) by the risk of the event in the control group. RRs less than 1.0 will be defined to favour the experimental group (that is fewer adverse events than in the comparator group) and RRs greater than 1.0 will be defined to favour the comparator group (Higgins 2011).

Unit of analysis issues

Special issues in the analysis of studies with non-standard designs will be handled according to the suggestions of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For cross-over trials, paired data will be analysed if available. Elsewise, only data from the first active treatment phase will be used. If repeated outcome assessments are presented, the time frames will

be defined as short term (up to six months), medium term (six to 12 months), and long term follow-up (more than 12 months). For studies that contribute multiple, correlated comparisons, all relevant experimental intervention groups of the study (for example groups with yoga interventions of different intensities) will be combined into a single group and all comparable relevant control intervention groups (for example groups with exercise interventions of different intensities) will be combined into a single control group. Control groups with different types of interventions (for example waiting list control and exercise) will not be combined in a single meta-analysis but analysed separately.

Dealing with missing data

Where standard deviations are missing, they will be calculated from standard errors, confidence intervals, or t values, or attempts will be made by e-mail to obtain the missing data from the trial authors (Higgins 2011). If these data are not available, the missing standard deviation will be substituted with the mean of the standard deviations of available studies which used the same outcome scale. Where means are missing, attempts will be made by e-mail to obtain the missing data from the trial authors.
Sensitivity analyses will be conducted by excluding studies where missing data had to be substituted (see below).
The potential impact of missing data on the findings of the review will be discussed in the 'Discussion' section.

Assessment of heterogeneity

Statistical heterogeneity between studies will be assessed using the Chi^2 test (Cochran 1954). A P value $\leq$ 0.10 will be regarded to indicate significant heterogeneity. Additionally, the I^2 statistic (Higgins 2003) will be used. The magnitude of heterogeneity will be categorized as: I^2 = 0% to 24%, low heterogeneity; I^2 = 25% to 49%, moderate heterogeneity; I^2 = 50% to 74%, substantial heterogeneity; and I^2 = 75% to 100%, considerable heterogeneity.

Assessment of reporting biases

If at least 10 studies are included in a meta-analysis, funnel plots of effect estimates against their standard errors (on a reversed scale) will be generated using Review Manager software (RevMan). Publication bias will be assessed by visual analysis of funnel plots, with roughly symmetrical funnel plots indicating low risk and asymmetrical funnel plots indicating high risk of publication bias (Higgins 2011). One should be aware that funnel plot asymmetry might also arise from other sources, and that publication bias need not lead to asymmetry in the funnel plots. Further attempts will be made to avoid publication bias by searching trial registries and conference proceedings for unpublished studies.
Duplicate publication bias will be addressed as studies with more than one publication will be included only once. If there is doubt whether multiple publications refer to the same data, attempts will be made to contact the trial authors by e-mail.
Location bias will be addressed by searching multiple databases, including one of Indian journals, and by including non-English language journals.
Language bias will be avoided by including studies irrespective of the language of publication.

Data synthesis

For continuous outcomes, data will be pooled using a random-effects model (inverse variance method). For dichotomous outcomes, a random-effects model (DerSimonian and Laird) will be used. All analyses will be performed using RevMan 5 software (RevMan).
To grade the quality of evidence, the GRADE approach will be used (Brozek 2009). The software GradePro will be used. A 'Summary of findings' table will be created to present the evidence for the primary outcomes (health-related quality, depression, anxiety, fatigue, and sleep disturbances).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be conducted for the following.
I) Current treatment status:
1. women with breast cancer undergoing active cancer treatment (radiotherapy or chemotherapy);
2. women who have completed active treatment.

II) Time since diagnosis:
1. women with breast cancer diagnosed $\leq$ five years before time of study entry;
2. women with breast cancer diagnosed > five years before time of study entry.

III) Stage of cancer:
1. metastatic breast cancer at time of study entry;
2. non-metastatic breast cancer at time of study entry.

Further subgroup analyses will be conducted for the type of yoga intervention:
1. complex yoga interventions including physical exercise and at least one of the following: breath control, meditation, and lifestyle advice (based on yoga theory or traditional yoga practices);
2. exercise-based yoga interventions (based on yoga theory or traditional yoga practices) without breath control, meditation, or lifestyle advice;
3. meditation-based yoga interventions including at least one of the following: breath control, meditation, and lifestyle advice (based on yoga theory or traditional yoga practices) without an exercise component.

Subgroup differences will be tested using the Chi^2 test for heterogeneity across subgroups. The I^2 statistics for subgroup differences will be computed as the percentage of the variance between the

different subgroups that is due to genuine subgroup differences rather than chance (Higgins 2011).

If statistical heterogeneity is present in the respective meta-analysis, subgroup and sensitivity analyses will also be used to explore possible reasons for the heterogeneity.

Sensitivity analysis

Sensitivity analyses will be performed by subsequently excluding studies with inadequate random sequence generation, studies with inadequate allocation concealment, studies without blinding of outcome assessors, and studies with high risk of attrition bias. Further sensitivity analyses will be performed by excluding studies where missing data had to be substituted and by excluding studies that were unpublished or published only in abstract format.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE

#1 yoga [mh]
#2 yoga* [tiab]
#3 yogic [tiab]
#4 meditation [tiab]
#5 asana* [tiab]
#6 pranayama [tiab]
#7 dharana [tiab]
#8 dhyana [tiab]
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 breast neoplasms [mh]
#11 breast neoplasm* [tiab]
#12 breast cancer [tiab]
#13 breast carcinoma* [tiab]
#14 breast tumor* [tiab]
#15 mamma carcinoma* [tiab]
#16 mammary neoplasm* [tiab]
#17 mammary carcinoma* [tiab]
#18 mammary gland carcinoma* [tiab]
#19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 randomized controlled trial [pt]
#21 controlled clinical trial [pt]
#22 randomized [tiab]
#23 placebo [tiab]
#24 clinical trials as topic [mesh: noexp]
#25 randomly [tiab]
#26 trial [ti]
#27 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28 Search #7 AND #17 AND #25
#29 Search animals[mh] NOT humans[mh]
#30 Search #26 NOT #27

Appendix 2. EMBASE

#1
randomised AND **controlled** AND **trial**
#2
randomized AND **controlled** AND **trial**
#3
controlled AND **clinical** AND **trial**
#4
randomi*ed:ab
#5
placebo:ab
#6
randomly:ab
#7
trial:ab
#8
groups:ab
#9
#1 OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR #7 OR **#8**
#10
'breast neoplasm'
#11
'breast cancer'/exp OR **'breast cancer'**
#12
'breast tumour'
#13
'breast tumor'/exp OR **'breast tumor'**
#14
'breast carcinoma'/exp OR **'breast carcinoma'**
#15
'mamma carcinoma'/exp OR **'mamma carcinoma'**
#16
'mammary neoplasm'
#17
'mammary carcinoma'/exp OR **'mammary carcinoma'**
#18
'mammary gland carcinoma'
#19
#10 OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18**
#20
'breast cancer survivor'
#21
'breast cancer survivors'
#22
#20 OR **#21**
#23
#19 OR **#22**
#24
'yoga'/exp OR **yoga**
#25
yogic
#26

meditation
#27
asana
#28
pranayama
#29
dharana
#30
dhyana
#31
#24 OR **#25** OR **#26** OR **#27** OR **#28 OR #29 OR #30**
#32
#9 AND **#23** AND **#29**
#33
#30 AND [humans]/lim AND [embase]/lim

Appendix 3. WHO ICTRP search portal

Basic searches:
1. Yoga for women with breast cancer and breast cancer survivors
2. Breast cancer AND yoga
3. Breast cancer survivors AND yoga
Advanced searches:
1. Title: Yoga for women with breast cancer and breast cancer survivors
Recruitment Status: ALL
2. Condition: breast cancer
Intervention: yoga OR yogic OR meditation OR asana OR pranayama OR dharana OR dhyana
Recruitment Status: ALL
3. Condition: breast cancer survivor*
Intervention: yoga OR yogic OR meditation OR asana OR pranayama OR dharana OR dhyana
Recruitment Status: ALL
4. Condition: breast cancer AND survivor
Intervention: yoga OR yogic OR meditation OR asana OR pranayama OR dharana OR dhyana
Recruitment Status:
ALL

Appendix 4. Clinicaltrials.gov

Basic searches:
1. Yoga for women with breast cancer and breast cancer survivors
2. Breast cancer AND yoga
3. Breast cancer survivors AND yoga
Advanced searches:
1. Title: Yoga for women with breast cancer and breast cancer survivors
Recruitment: ALL
Study Results: ALL
Study Type: ALL
Gender: ALL
2. Condition: breast cancer
Intervention: yoga OR yogic OR meditation OR asana OR pranayama OR dharana OR dhyana
Recruitment: ALL
Study Results: ALL

Study Type: ALL
Gender: ALL
3. Condition: breast cancer survivor
Intervention: yoga OR yogic OR meditation OR asana OR pranayama OR dharana OR dhyana
Recruitment: ALL
Study Results: ALL
Study Type: ALL
Gender: ALL
4. Condition: breast cancer AND survivor
Intervention: yoga OR yogic OR meditation OR asana OR pranayama OR dharana OR dhyana
Recruitment: ALL
Study Results: ALL
Study Type: ALL
Gender: ALL

Appendix 5. IndMed

(yoga OR yogic OR meditation OR asana OR asanas OR pranayama OR dharana OR dhyana) AND (breast neoplasm OR breast neoplasms OR breast cancer OR breast carcinoma OR breast carcinomas OR breast tumor OR breast tumors OR mamma carcinoma OR mamma carcinomas)

Appendix 6. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast cancer survivor*
#3 #1 or #2
#4 yoga or yogic or meditation or asana or pranayama or dharana or dhyana
#5 #3 and #4

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: HC
2. Study selection: HC, RL, PK
3. Extract data from studies: SL, PK, HC
4. Enter data into RevMan: HC
5. Carry out the analysis: HC
6. Interpret the analysis: HC, RL, JL, GJD
7. Draft the final review: HC
8. Disagreement resolution: HC, PK
9. Update the review: HC, RL

DECLARATIONS OF INTEREST

None known

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