Rebecca P. George, Ines Semendric, Eleanor R. Bowley-Schubert, Christine T. Chivonivoni, Alexandra P. Warrender, Alexandra L. Whittaker

Reporting in rodent models of 'chemobrain': a systematic review assessing compliance with the ARRIVE guidelines

Supportive Care in Cancer, 2021; 29(11):7073-7084

Reporting in Rodent Models of 'Chemobrain': a Systematic Review Assessing Compliance with the ARRIVE Guidelines

Rebecca P George[a,*], Ines Semendric [b], Eleanor R Bowley-Schubert [b], Christine T Chivonivoni [b], Alexandra P Warrender [b], Alexandra L Whittaker[a,*]

[a] School of Animal and Veterinary Sciences, The University of Adelaide, Roseworthy Campus, Roseworthy, South Australia 5371, Australia

[b] Adelaide Medical School, The University of Adelaide, Adelaide, South Australia 5005, Australia

[*] Corresponding Authors Emails: rebecca.george@adelaide.edu.au; alexandra.whittaker@adelaide.edu.au

Abstract

Patients diagnosed with cancer are often plagued with debilitating side effects post chemotherapy treatment. One such side effect is chemotherapy-induced cognitive impairment or 'chemobrain'. Rodent models are commonly used to investigate pathogenesis and potential therapeutic strategies. However, concerns have been raised regarding inadequacies in reporting of animal studies rendering them unreliable and irreproducible. The aim of this systematic review was to assess compliance with the ARRIVE reporting guidelines in peer-reviewed publications evaluating chemotherapy-induced cognitive changes in rodent models, and to determine if the introduction of the ARRIVE guidelines has improved quality of reporting. A comprehensive search was conducted to identify relevant peer reviewed publications. Ninety-seven studies met the eligibility criteria and publication compliance with the ARRIVE guidelines reporting was assessed. No studies achieved full adherence with the ARRIVE guidelines. Furthermore, no significant improvement was demonstrated in the overall compliance score post-ARRIVE. Given the lack of standardisation of animal models in this research area, these results pose particular threat to future progress and translation of findings in this area of research. These results highlight the need for stricter adherence to the ARRIVE guidelines by journal editors and reviewers. Animal Ethics Committees also have an important educative role in improving knowledge and awareness of the guidelines amongst researchers.

Keywords chemobrain; CICI; cognitive impairment; ARRIVE, reporting guidelines

Introduction

The development of new, diverse chemotherapeutic agents for cancer therapy has led to a considerably reduced reoccurrence and higher survival rates for numerous types of cancer [39].

Despite this relative success, patients are often plagued with undesirable, debilitating side effects arising from treatment, resulting in forced dose reduction or even cessation of treatment [37]. Chemotherapy agents act to prevent cancer cell multiplication in surrounding tissues whilst limiting overall cell proliferation. However, this process is non-specific and toxic effects on normal functioning cells are common. The CNS is particularly vulnerable to toxicity resulting in a condition colloquially termed 'chemobrain'[32]. Chemotherapy-induced cognitive impairment (CICI) or 'chemobrain' is a condition that has been associated with chemotherapy administration and may affect up to 75% of patients for around 2 years following treatment courses, with around 35% of those patients experiencing deficits lasting some decades [1, 32]. However, despite the condition name, cognitive impairment can also arise as a result of other common cancer treatment modalities, such as cranial radiation and hormonal therapy. There is also evidence that cancer itself causes impairments, either through direct effects or linked to associated factors such as fatigue and distress [11, 28, 38]. Common side effects include deficiencies in attention, language, memory and executive function, as well as fatigue, psychomotor function and motivational deficits [16, 24, 37, 40]. These symptoms have been consistently observed across all cancer types, including those not of CNS origin where direct effects on brain tissue are expected [15, 16]. Cognitive impairments can have a significant impact on activities of daily life, employment, leisure and maintenance of relationships [10, 15]. Chemobrain thus presents a significant personal and societal burden, especially as cancer survivorship increases. In recognition of the implications of chemobrain for survivor quality of life post-treatment, multiple existing survivorship frameworks have identified the need for greater understanding of the pathogenesis underlying chemobrain, as well as the development of treatment and mitigation options, as priorities for research [23].

Patient research plays a key role in understanding the prevalence, severity and lived experience of this condition [3, 7, 21, 22, 26, 31]. However, interpretation of patient data can be challenging, due to the number of confounding factors inherent in observational study designs, including patient age, cancer type, treatment administered, presence of comorbidities, disease progression, pre-treatment cognitive status, as well as experiences of anxiety or depression [8, 18, 29, 34]. These factors, as well as the need for invasive tissue collection, mean that clinical studies are often not ideal for gaining mechanistic understanding of chemobrain, or in early-stage testing of therapeutics. Animal studies are therefore used since they allow control of extraneous variables, such as genetics and tumour status. As a result, the majority of pre-clinical studies of chemobrain use a rodent model [30].

Whilst rodent models are primarily utilised in 'chemobrain' research, concerns have been raised in recent years about the extent of inadequate reporting of animal studies, consequently rendering them unreliable and irreproducible [2, 20, 35]. Incomplete descriptions of methodological items, as well as inappropriate or incomplete reporting of data raise scientific, ethical and economic concerns. Therefore, transparent reporting of methods and results is a vital component in increasing reproducibility of findings [5]. In an attempt to address these concerns, The ARRIVE (Animals in Research: Reporting in vivo Experiments) guidelines were released in June 2010 [12]. These guidelines aimed to universally improve the quality of animal reporting, increase transparency of findings and ultimately allow for greater reproducibility and translation of results of animal studies [5, 12]. Landis and colleagues in 2012 further refined the list to four key attributes that should be reported on at a minimum. Randomisation, blinding, sample-size estimation and data handling were deemed to be universally accepted as core issues impacting on study evaluation [14]. The ARRIVE guidelines were updated in 2020 by reorganizing items to facilitate their use [25]. The current guidelines are organized into two sets, comprising an essential ten that should be included as a minimum in any publication where animal research was performed, and a recommended set to complement these. Reporting of the items in both sets represents best practice, and should be the ultimate goal. The guidelines also consist of a simple checklist summarizing the minimum information required. This document is designed to aid authors when preparing manuscripts, and allow journal reviewers and editors to simply confirm compliance with guidelines [25].

In comparison to other more established pre-clinical research areas, there is greater variability in animal models for chemobrain, with no established 'standard' model [4, 18]. Furthermore, outcomes assessed are heterogeneous and commonly include results of a range of behavioural tests which are known to be highly variable both within and between animals [6]. This variability makes accurate and transparent reporting, especially of animal-related characteristics, even more important in this area of research to enhance opportunities for translation of findings to clinical settings. Therefore, the goal of this systematic review was to assess compliance with the ARRIVE guidelines in scientific publications evaluating chemotherapy-induced cognitive changes in rodent models. The secondary aim was to determine if the introduction of the ARRIVE guidelines has made an impact on quality of reporting.

Methods

Search Strategy

A comprehensive search was conducted using Medline via PubMed and Scopus to identify relevant peer reviewed publications. The search strategy consisted of terms such as "chemotherapy", "anti-cancer agents", "animal models", "cognitive impairment", "cancer induced cognition changes" and related synonyms (refer to supplementary material S1). The search was conducted in August 2020. Independent reviewers (CC, AW, and EB) screened articles based on pre-defined inclusion and exclusion criteria and any conflicts were resolved by discussion. The third reviewer was consulted if a consensus could not be met.

Inclusion and Exclusion Criteria

In order to be considered for review, the articles were required to meet the following criteria: [1] original full text articles available from database; [2] use of a rat/mouse model regardless of strain, sex or age; [3] administration of cancer chemotherapy agent regardless of route of administration or dosage, to naïve, cancer-inoculated, or tumour-inoculated animals; [4] studies that evaluated chemotherapy-induced cognitive impairment via either behavioural or tissue based measures or combination thereof; [5] English language publications.

The exclusion criteria for articles were as follows: abstracts and conference proceedings, review articles, use of non-rat/mouse animal models or human clinical studies, studies that did not assess chemotherapy-induced cognitive impairment, and non-English publications.

Search Results

The database search identified a total of 638 studies. All citations were uploaded to EndNote (EndNote ™ X9) and then imported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) where duplicates were automatically identified, removed and manually cross referenced. The remaining studies were screened based on title and abstract against the pre-defined inclusion and exclusion criteria by three independent reviewers (CC, AW, and EB). A total of 399 studies were excluded based on title and abstract screening, with 117 studies remaining for full text assessment.

Full texts were manually retrieved and imported into Covidence. Three independent reviewers thoroughly assessed the studies by full text for their eligibility. During the eligibility

process, 20 studies were excluded due to not being an original full text article, not assessing chemotherapy agents, not utilising a rodent model and full text being unavailable**.** Details of the identification process are described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

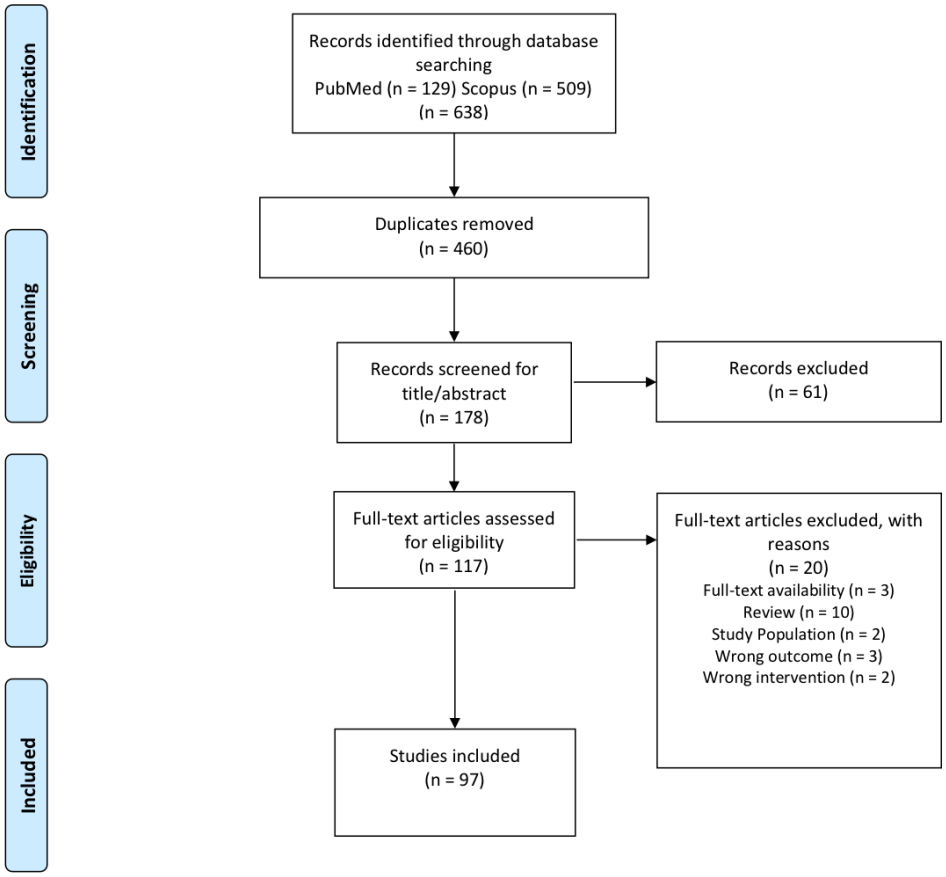

Figure 1. PRISMA flow diagram for the review process [19].

Data Extraction

Data were extracted from 97 included studies by two independent reviewers (RG and IS) with a third independent reviewer consulted if necessary (A.L.W). Prior to data extraction two reviewers independently extracted data from two studies to ensure uniformity in the reviewing process. To assess publication compliance with the ARRIVE guidelines reporting was assessed at an item and sub-item level (table 1), namely ethical statement (item 5), study design (item 6a and 6b), experimental procedures (item 7a, 7b, 7c and 7d), experimental animals (item 8), housing and husbandry (item 9a and 9b), sample size (item 10a and 10b), allocating animals to experimental groups (item 11a), statistical methods (item 13a), baseline

data (item 14), numbers analysed (item 15a), outcomes and estimations (item 16) and adverse events (item 17a and 17b). Each included study was critically appraised for compliance with the guidelines for the items with a rating score from 0-2 assigned (0 = not reported; 1 = partially reported, 2 = reported) (table 1). In addition, item 6b (blinding) was differentiated to item 11a (randomisation of animal allocation to treatment group) as blinding may include randomisation as a method of reducing subjective bias. Since ethical statement (item 5) and adverse events (item 17a and 17b) can only be scored in a binary fashion (yes or no), these items were either allocated a 0 or a 1 by the independent reviewers and this is reflected in the total score. For visualisation of data these items were classified as '0 = not reported' and '2 = reported'. The rating score for each ARRIVE guideline item was summed to produce a total compliance score out of 36. Information regarding citation information (authors, year of publication, titles, country of corresponding author) was also extracted. Additionally, in order to determine if the introduction of the ARRIVE guidelines has made an impact on quality of reporting, included studies were divided into two groups; pre-introduction of the ARRIVE guidelines (pre-ARRIVE) and post- introduction of the ARRIVE guidelines (post-ARRIVE). Extracted data were cross-checked and verified by two independent reviewers.

Statistical Analysis

The statistical analysis was performed utilising IBM SPSS (SPSS Inc., Chicago, IL, USA) statistical software. Data were tested for normality and homogeneity of variance utilising the Shapiro-Wilk test. A repeated measures ANOVA was performed to determine changes in reporting across years. Due to unequal variance between groups compliance scores pre- and post- ARRIVE guidelines were compared using a Welch's t-test. Statistical significance was determined at $p < 0.05$.

Table 1. Rating score used to evaluate the quality of reporting in rodent models of chemobrain based on the ARRIVE Guidelines

Category	Item	Recommendation Description	Rating score
Methods			
Ethical statement	5	Ethical statement	0 – not reported 1 – reported
Study Design	6a	The number of experimental and control groups.	0 – not reported 1 – partially reported 2 – reported
	6b	Blinding - minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. blinded observer).	0 – not reported 1 – partially reported 2 – reported
Experimental procedures	7a	How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used). Details of any specialist equipment used, including supplier(s).	0 – not reported 1 – partially reported 2 – reported
	7b	When (e.g. time of day).	0 – not reported 1 – partially reported 2 – reported
	7c	Where (e.g. home cage, laboratory, water maze).	0 – not reported 1 – partially reported 2 – reported
	7d	Why (e.g. rationale for choice of procedures)	0 – not reported 1 – partially reported 2 – reported
Experimental animals	8a	Animal characteristics (including species, strain, sex, developmental stage and weight	0 – not reported 1 – partially reported 2 – reported
Housing and husbandry	9a	Housing (type of facility, type of cage or housing; bedding material; number of cage companions)	0 – not reported 1 – partially reported 2 – reported
	9b	Husbandry conditions (e.g. light/dark cycle, temperature, access to food and water, environmental enrichment).	0 – not reported 1 – partially reported 2 – reported
	9c	Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.	0 – not reported 1 – partially reported 2 – reported
Sample size	10a	Total number of animals used in each experiment, and the number of animals in each experimental group.	0 – not reported 1 – partially reported 2 – reported
	10b	Explain how the number of animals was arrived at. Details of any sample size calculation used.	0 – not reported 1 – partially reported 2 – reported
Allocating animals to experimental groups	11a	Randomisation - Details of how animals were allocated to experimental groups, including randomisation or matching if done.	0 – not reported 1 – partially reported 2 – reported
Statistical methods	13a	Details of the statistical methods used for each analysis.	0 – not reported 1 – partially reported 2 – reported
	13c	Methods used to assess whether the data met the assumptions of the statistical approach.	
Results			
Baseline data	14	For each experimental group, relevant characteristics and health status of animals (e.g. weight, microbiological status, and drug or test naïve) prior to treatment or testing.	0 – not reported 1 – partially reported 2 – reported
Numbers analysed	15a	Number of animals in each group included in each analysis. Report absolute numbers.	0 – not reported 1 – partially reported 2 – reported
Outcomes and estimation	16	Results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).	0 – not reported 1 – partially reported 2 – reported
Adverse events	17a	Details of all important adverse events in each experimental group.	0 – not reported 1 – reported

Results

Descriptive characteristics of included studies

A total of 97 studies met the eligibility criteria and were included in this review. The publication dates ranged from 2008 to 2020, with 88.7% (86 studies) of the included studies being published after the ARRIVE Guidelines were published in June 2010. Data were provided from 19 countries; Canada (n=7), United States (n=43), China (n=12), Brazil (n=2), The Netherlands (n=2), United Kingdom (n=3), Australia (n=7), Egypt (n=1), Republic of Korea (n=7), France (n=2), Japan (n=1), Ireland (n=1), Amsterdam (n=1), Chile (n=1), Germany (n=1), India (n=2), Saudi Arabia (n=1), Thailand (n=2) and Slovakia (n=1) (Figure 2).

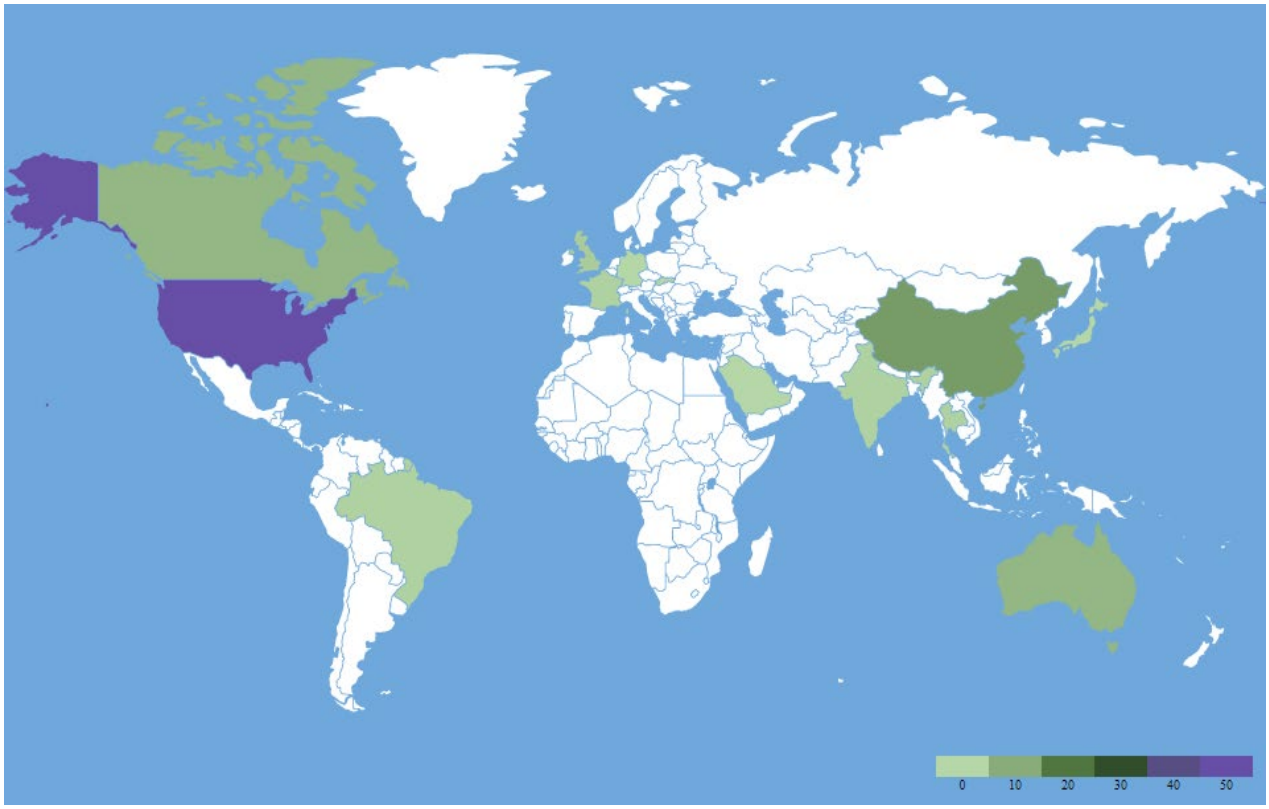

Figure 2. World heat map depicting geographical location of corresponding author of included studies.

Overall compliance score

To achieve 100% compliance, the included studies had to fully report each item and sub-item included in the evaluation (Table 1). A total of 12 items comprising 20 sub-items concerning reporting in the Methods and Results sections were evaluated in this study. None of the included studies achieved full adherence with the ARRIVE guidelines. Further, no significant improvement was demonstrated in the overall compliance score post-ARRIVE

($t_{13.593}$ = 2.021, p = 0.063). The mean compliance score rated out of 36 for pre-ARRIVE and post-ARRIVE was less than 70% (pre-ARRIVE, mean compliance score 22.36; post-ARRIVE, mean compliance score 24.58) (Figure 3A). Out of the items evaluated only the outcomes and estimations (item 16) were reported in 100% of the included studies, both pre-ARRIVE and post-ARRIVE (Figure 3B). Overall compliance rating for each sub-item for Pre-ARRIVE and Post-ARRIVE guidelines are displayed in Figure 5 and Figure 6, respectively. There were no statistically significant differences observed between the overall reporting compliance across the years published (F (14, 82) = 0.7200, p = p = 0.7485) (Figure 4).

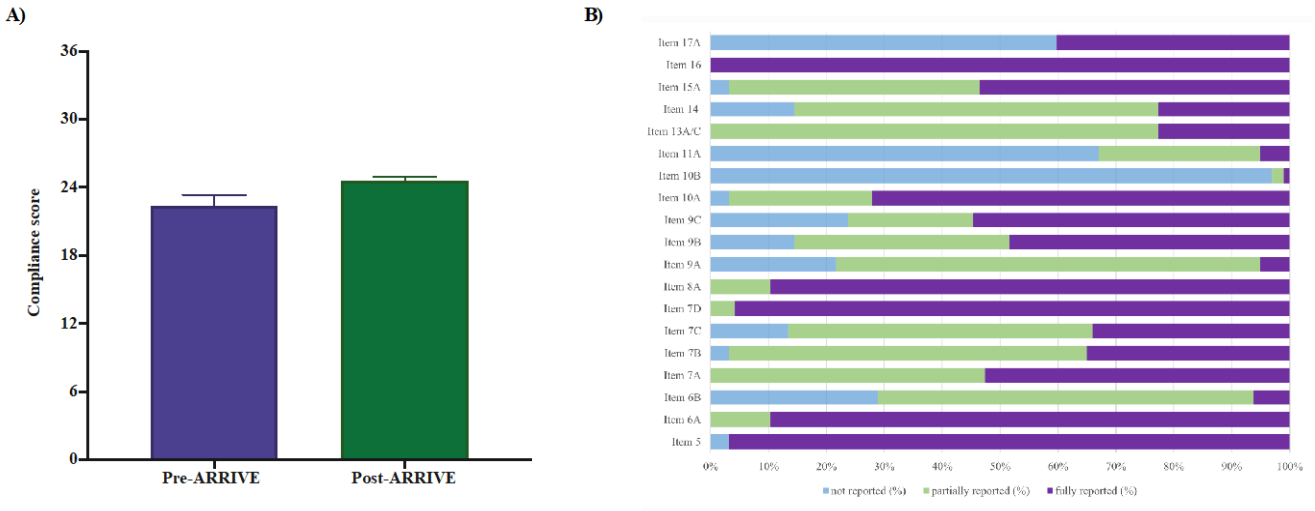

Figure 3. A) Mean compliance score of studies pre-ARRIVE and post-ARRIVE. *N = 97*, B) Percentage (%) of items not reported, partially reported, and fully reported for each ARRIVE item analysed.

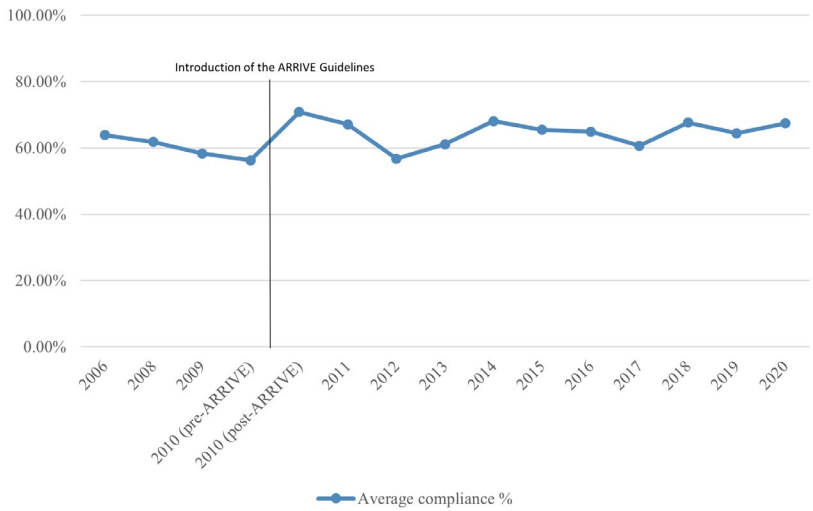

Figure 4. Mean adherence (%) with the ARRIVE guidelines of included studies ranging from 2006-2020 visualising the introduction of the ARRIVE Guidelines in July 2010.

Per-item analysis

Item 5 – ethical statement

Overall, 3.1% of studies reported no ethical statement and 96.9% of studies fully reported an ethical statement. In studies published pre-ARRIVE, 18.2% reported no ethical statement and 81.8% reported an ethical statement. In contrast, in studies published post-ARRIVE 1.2% reported no ethical statement and 98.8% reported an ethical statement.

Item 6a and 6b – study design

It was found that 10.3% of studies partially reported the number of experimental and control groups (item 6a), and 89.7% of studies fully reported. In studies published pre-ARRIVE, 27.3% partially reported and 72.7% fully reported this item, while in studies published post-ARRIVE 8.1% partially reported and 91.9% fully reported. Overall, 28.9% of studies did not report blinding procedures, 65% partially reported, and 6.2% fully reported. Of these studies, those published pre-ARRIVE, 54.6% did not report and 45.5% partially reported. In contrast, in post-ARRIVE studies 25.6% did not report, 67.4% partially reported, and 7% fully reported.

Item 7a, 7b, 7c, and 7d – experimental procedures

Overall, 47.4% of studies partially reported full experimental procedures (item 7a), and 52.6% fully reported. Of these, 63.6% of pre-ARRIVE studies partially reported and 36.4% fully reported. 45.4% of post-ARRIVE studies partially reported and 54.7% fully reported. In general, 3.1% of studies did not report when procedures were conducted (item 7b), 61.9% partially reported, and 35.1% fully reported. Of these, 72.73% of pre-ARRIVE studies partially reported and 27.3% fully reported. 3.5% of post-ARRIVE studies did not report, 60.5% partially reported, and 36.1% fully reported. Overall, 13.4% of studies did not report where procedures were conducted (item 7c), 52.6% partially reported, and 34% fully reported. Of these, 54.6% of pre-ARRIVE studies partially reported, and 45.5% fully reported. It was discovered that 15.1% of post-ARRIVE studies did not report, 52.3% partially reported, and 32.6% fully reported. Study rationale (item 7d) was partially reported in 4.1% of studies and

95.9% fully reported. Of the pre-ARRIVE studies 9.1% partially reported, and 90.9% fully reported, while 3.5% of post-ARRIVE studies partially reported, and 96.5% fully reported.

Item 8a – experimental animals

Animal characteristics (item 8a) were fully reported in 95.9% of studies and partially reported in 4.1% of overall studies. Pre-ARRIVE studies fully reported in 100% of studies, while 11.6% of post-ARRIVE studies partially reported, and 88.4% fully reported.

Item 9a, 9b, and 9c – housing and husbandry

Overall, 21.7% of studies did not report housing conditions (item 9a), 73.2% partially reported, and 5.2% fully reported. It was found that 18.2% of pre-ARRIVE studies did not report, 72.7% partially reported, and 9.1% fully reported. Also, 22.1% of post-ARRIVE studies did not report, 73.3% partially reported, and 4.7% fully reported. Overall, 14.4% of studies did not report husbandry conditions (item 9b), 37.1% partially reported, and 48.5% fully reported. Of these 63.6% of pre-ARRIVE studies partially reported, and 36.4% fully reported, while 16.3% of post-ARRIVE studies did not report, 33.7% partially reported, and 50% fully reported. Overall, 23.7% of studies did not report welfare related assessments and interventions (item 9c), 21.7% partially reported, and 54.6% fully reported. Of the pre-ARRIVE studies, 54.6% did not report, 9.1% partially reported, and 36.4% fully reported. Alternatively, 19.8% of post-ARRIVE studies did not report, 23.3% partially reported, and 57% fully reported.

Item 10a and 10b – sample size

It was found that 3.1% of studies did not report total number of animals used in each experiment and in each experimental group (item 10a), 24.7% partially reported, and 72.2% fully reported. Of the pre-ARRIVE studies, 45.5% partially reported and 54.6% fully reported, while 3.5% of post-ARRIVE studies did not report, 22.1% partially reported, 74.4% fully reported. Overall, 96.9% of studies did not report sample size calculation (item 10b), 2.1% partially reported, and 1% fully reported. Furthermore, 100% of pre-ARRIVE studies did not report. 96.5% of post-ARRIVE studies did not report, 2.3% partially reported, and 1.2% fully reported.

Item 11a – allocation of animals to experimental groups

Overall, 67% of studies did not report randomisation details for group allocation, 27.8% partially reported, and 5.2% fully reported. It was found that 72.7% of pre-ARRIVE studies did not report, 18.2% partially reported, and 9.1% fully reported, while 66.3% of post-ARRIVE studies did not report, 29.1% partially reported, and 4.7% fully reported.

Item 13a/c – statistical methods

The vast majority of studies (77.3%) partially reported details of statistical methods (item 13a) and methods used to assess if data approached statistical significance (item 13c), 22.7% fully reported. Overall, 81.8% of pre-ARRIVE studies partially reported, and 18.2% fully reported. Similarly, 76.7% of post-ARRIVE studies partially reported, and 23.3% fully reported.

Item 14 – baseline data

It was found that 14.4% of studies did not report relevant characteristics or health status prior to testing/treatment (item 14), 62.9% partially reported, and 22.7% fully reported. In total 18.2% of pre-ARRIVE studies did not report, 72.7% partially reported, and 9.1% fully reported. Comparably, 14% of post-ARRIVE studies did not report, 61.6% partially reported, and 24.4% fully reported.

Item 15a – numbers analysed

Overall, 3.1% of studies did not report number of animals from each group included in analysis (item 15a), 43.3% partially reported, and 53.6% fully reported. It was also determined that 9.1% of pre-ARRIVE studies did not report, 63.6% partially reported, and 27.3% fully reported, while 2.3% of post-ARRIVE studies did not report, 40.7% partially reported, and 57% fully reported.

Item 16 – outcomes and estimation

It was shown that 100% of pre-ARRIVE and post-ARRIVE studies reported results for each analysis carried out reported with precision (item 16).

Item 17a – adverse events

Overall, 59.8% of studies did not report adverse events (item 17a), and 40.2% fully reported. Furthermore, 72.7% of pre-ARRIVE studies did not report, and 27.3% fully reported.

Comparably, a total of 58.1% of post-ARRIVE studies did not report, while 41.9% fully reported.

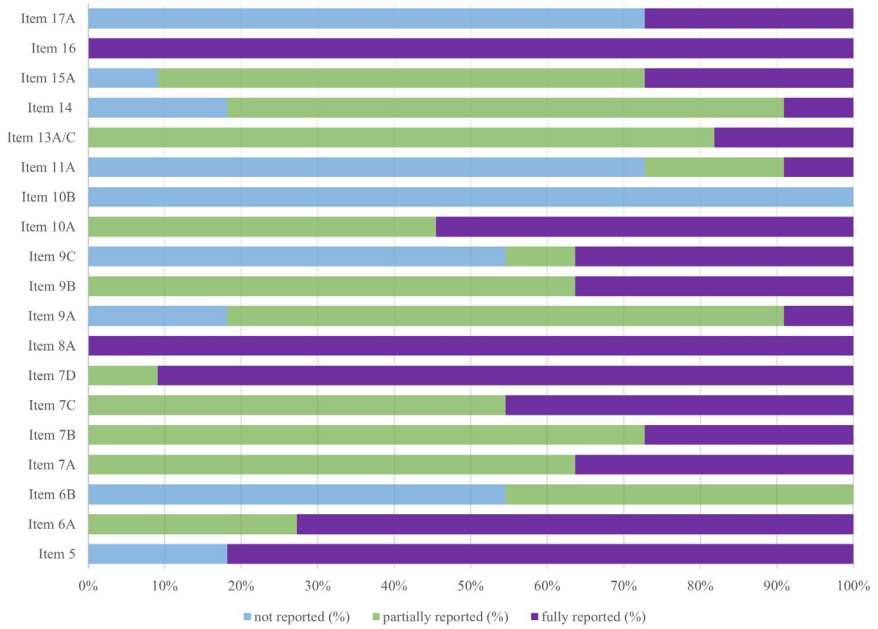

Figure 5. Percentage (%) of items not reported, partially reported, and fully reported for each ARRIVE item analysed pre-ARRIVE. *N = 11*.

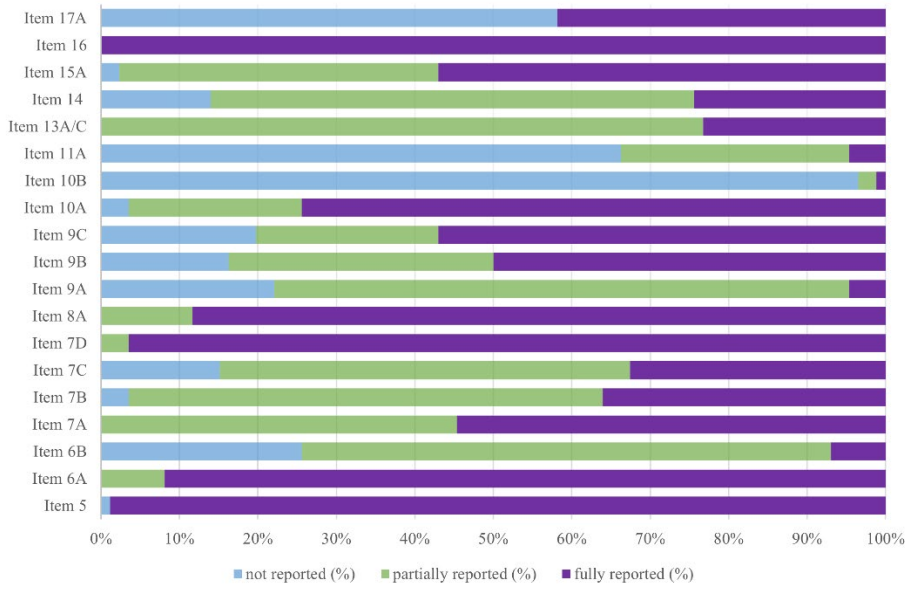

Figure 6. Percentage (%) of items not reported, partially reported, and fully reported for each ARRIVE item analysed post-ARRIVE. *N = 86.*

Discussion

Quality and consistency of reporting in animal-based studies is vital for the replication of results, translation of findings to the clinic, and to ensure resource investment in this type of research is not wasted. This is especially so in research areas such as CICI, where animal models are less well-defined and there is considerable heterogeneity of approach. The ARRIVE guidelines are generally regarded as the benchmark for this reporting, being the most widely accepted by a range of journals publishing pre-clinical animal studies [5]. It is therefore surprising that in spite of the widespread purported journal adherence to these standards no articles achieved full adherence with these guidelines.

Our results illustrate that out of the ARRIVE subitems evaluated few were reported well and in complete adherence with the ARRIVE guidelines, indicating considerable room for improvement. Outcomes and estimations (item 16), ethical statement (item 5), study rationale (item 7d) and animal characteristics (item 8a) were reported in more than 90% of the articles. It is suggested that these items may be well reported due to being recognised and well taught elements of study design and reporting, which most researchers are au fait with, or are enforced during journal submission processes (ethical statement). For example, researchers often have a good grounding in statistics and presentation of data through formal training, and are aware of the importance of making clear the 'knowledge gap' and study rationale through their experiences in grant writing and acquiring ethical approvals. However, other critical elements in reducing bias were less well reported. In consideration of only some of the key reporting attributes which make up the Landis 4 and the ARRIVE essential list, that of randomisation, blinding, and sample-size estimation, in spite of the weight placed on their reporting by these sets of guidelines, adherence was poor.

Although an essential element in reducing bias, randomisation (item 11a) was not mentioned in 67% of articles. Even when randomisation was documented, there was rarely a description of how the randomisation was conducted in order to produce truly comparable groups at selection, or for detection of outcomes. This lack of randomisation can lead to significant risk of introduction of bias. Complete reporting of the nature of randomisation is a key element of appraisal when using the SYRCLE Risk of Bias Tool for quality assessment of animal studies [9]. Other articles have reported similar findings, with Gulin et al., 2015 finding poorer reporting than shown here with only 7 out of 44 (16%) publications reporting on randomization in animal models for Chagas disease [5]. Randomization should also extend further than animal allocation to groups, considering cage placement within rooms, and order of experimental treatments or performance of assays.

Blinding similarly is crucial in terms of reducing bias, however a considerable percentage of studies did not include, or only partially reported this criterion (item 6b; 28.9%, 65% respectively). Blinding limits bias particularly when qualitative or subjective scoring of experimental observations is performed. This is likely to be especially important in studies in CICI which commonly include behavioural tests or assessment of clinical score where subjectivity can be introduced. Furthermore, true blinding should be feasible in CICI animal models, since the procedures involved tend not to lead to overt signs betraying the nature of group allocation. Our findings reflect previous literature with a survey undertaken across a range of pre-clinical research areas finding that blinding was not reported in 87% of cases [13].

Finally, whilst most authors reported the total number of animals used in each experimental group, the least presented criterion in our investigation was a sample size calculation on how this group size was derived. This went unreported in 96.9% of articles. This is perhaps unusual given the clinical linkages inherent in studies in this area; reporting of a power analysis is strictly enforced in human clinical trials and it might be assumed that researchers are engaged in both human and animal studies making power calculations second nature to them. Furthermore, applications for animal ethical approval often require the demonstration of a power analysis hence this non-compliance is likely to be a true case of non-reporting rather than non-consideration. Power calculations are essential to evaluation, statistical interpretation and replication of findings [13]. They also serve an important ethical role, ensuring prevention of unnecessary animal use, yet also ensuring that studies are not underpowered, hence animal lives being wasted. There is considerable heterogeneity in preclinical CICI studies resulting from aspects of experimental design, animal model choice, treatment procedures and nature of behavioural testing [40]. This is in addition to the variability that arises ordinarily in the use of preclinical animal models due to aspects such as husbandry, innate behaviour and the environment [39]. Improving reporting on methods would be beneficial in reducing the heterogeneity observed. Additionally, in relation to study attrition, differences in samples sizes were commonly observed between the Methods section and Results. This would suggest the occurrence of adverse events, yet these were infrequently reported (59.8% of articles). Adverse event reporting is probably even more important in CICI studies compared to other pre-clinical animal studies given the lack of standardisation of models. Full and accurate reporting is imperative to avoid future use of animal models that have a high welfare cost or that are not truly representative of the human condition.

The ARRIVE guidelines were introduced in 2010 in an attempt to address poor reporting, especially of critical items [12]. However, our findings suggest that their introduction has had little to no effect on the overall compliance in study reporting. Whilst, impacts of their implementation are expected to take some time to become apparent, over the 10-year passage of time since the guideline introduction this compliance trend has remained static. The ARRIVE guidelines 2.0 were introduced in an attempt to counteract poor compliance rates [25]. In the revised document, rewording to improve clarity and prioritization of certain criteria into the 'Essential 10' has been performed. It remains to be seen what impact these amended guidelines will have on compliance.

By its nature, we have only been able to make an assessment of reporting in this review. Reporting guidelines can only go so far in addressing issues of reproducibility and translatability, since many of the criteria require consideration in experimental planning and conduct. It is the need for pre-consideration of these items that is considered in planning guidelines such as the PREPARE (Planning Research and Experimental Procedures on Animals: Recommendations for Excellence) guidelines [33]. It is of course quite possible that researchers were using ARRIVE criteria but failing to report on these. In such cases, internal validity of the study would be preserved but the incomplete reporting is still a considerable threat to external validity or generalisation of the study findings to inform future work or allow translation. Furthermore, previous study has suggested that inadequate reporting correlates with overstatement of study outcomes [17, 36]. Use of both sets of guidelines will greatly increase the likelihood of translation success and adherence to the 3R's principles [33].

Lack of compliance with the guidelines may arise due to a lack of awareness of their existence, in which case there is a clear need for expanding the education of researchers, probably at the experiment planning stage. Animal Ethics Committees may be best placed to drive this education since they evaluate all protocols and have the ability to only allow protocols to proceed that meet their criteria. Referral to ARRIVE criteria in ethics application forms will not only ensure the criteria are addressed, but will serve to disseminate awareness of the concepts. At the other end of the research process, stricter adherence to the ARRIVE guidelines by journal editors and reviewers, along with the instigation of clear and unambiguous processes associated with them, such as submission of an ARRIVE checklist, will assist in improving reporting and provide a further educative function. This is especially appropriate given the establishment of the international cancer and cognition task force (ICCTF) which aims to

identify future research directions and provide recommendations to help standardise experimental design and procedures in animal models of CICI [41]. Improving the quality of reporting will also aid the production of systematic reviews, the means through which the weight of evidence in a particular area can be assessed [27].

Conclusion

The results from this systematic literature review reveal reporting of rodent models in relation to the ARRIVE guidelines rarely met the full set of essential criteria. Given the lack of standardisation of animal models in this research area, this is a particular threat to future progress and translation of findings. Furthermore, the lack of improvement since the guidelines introduction implies there is still a lack awareness or disbelief of the importance of this reporting. In the short term, this finding may be best remedied through the actions of journal editors and reviewers. In the longer term, the role that animal ethics committees play as the enablers of animal-based research should be considered.

Supplementary Information

Table S1; search strategy, citation details of included studies available on further request.

Author contribution

RPG designed the study, assisted in performing the literature search, data extraction, analysis and interpretation and writing the manuscript; IS assisted in study design, data extraction, analysis and interpretation and writing of the manuscript; CC, AW, EBS performed literature search and screened articles by title and abstract; AW involved in the study design, supervision of the development of the work, assisted in performing the literature search, data analysis and interpretation and writing of the manuscript.

Acknowledgements

This review was conducted with no external funding. ALW was supported by a NHMRC Peter Doherty Biomedical Research Fellowship (APP1140072). RPG was supported by an Australian Government Research Training Program Scholarship.

Conflict of interest

The authors declare no competing interests.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

References

1. Bagnall-Moreau C, Chaudhry S, Salas-Ramirez K, Ahles T, Hubbard K (2019) Chemotherapy-Induced Cognitive Impairment Is Associated with Increased Inflammation and Oxidative Damage in the Hippocampus Molecular Neurobiology 56: 7159-7172
2. Begley CG, Ellis LM (2012) Raise standards for preclinical cancer research Nature 483: 531-533
3. Cheung YT, Shwe M, Tan YP, Fan G, Ng R, Chan A (2012) Cognitive changes in multiethnic Asian breast cancer patients: a focus group study Annals of Oncology 23: 2547-2552
4. George RP, Semendric I, Hutchinson MR, Whittaker AL (2021) Neuroimmune reactivity marker expression in rodent models of chemotherapy-induced cognitive impairment: a systematic scoping review Brain, Behavior, and Immunity
5. Gulin JE, Rocco DM, García-Bournissen F (2015) Quality of Reporting and Adherence to ARRIVE Guidelines in Animal Studies for Chagas Disease Preclinical Drug Research: A Systematic Review PLoS Negl Trop Dis 9: e0004194
6. Hånell A, Marklund N (2014) Structured evaluation of rodent behavioral tests used in drug discovery research Frontiers in Behavioral Neuroscience 8
7. Henderson FM, Cross AJ, Baraniak AR (2019) 'A new normal with chemobrain': Experiences of the impact of chemotherapy-related cognitive deficits in long-term breast cancer survivors Health Psychol Open 6: 2055102919832234-2055102919832234
8. Hodgson KD, Hutchinson AD, Wilson CJ, Nettelbeck T (2013) A meta-analysis of the effects of chemotherapy on cognition in patients with cancer Cancer Treatment Reviews 39: 297-304
9. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW (2014) SYRCLE's risk of bias tool for animal studies BMC Medical Research Methodology 14: 43
10. Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C (2012) Objective and subjective cognitive impairment following chemotherapy for cancer: A systematic review Cancer treatment reviews 38: 926-934
11. Janelsins MC, Kesler SR, Ahles TA, Morrow GR (2014) Prevalence, mechanisms, and management of cancer-related cognitive impairment International Review of Psychiatry: The Interface of Psychiatry and Oncology GUEST EDITOR: M Beatriz Currier 26: 102-113
12. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG (2010) Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research PLOS Biology 8: e1000412
13. Kilkenny C, Parsons N, Kadyszewski E, Festing MF, Cuthill IC, Fry D, Hutton J, Altman DG (2009) Survey of the quality of experimental design, statistical analysis and reporting of research using animals PLoS One 4: e7824
14. Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, Bradley EW, Crystal RG, Darnell RB, Ferrante RJ, Fillit H, Finkelstein R, Fisher M, Gendelman HE, Golub RM, Goudreau JL, Gross RA, Gubitz AK, Hesterlee SE, Howells DW, Huguenard J, Kelner K, Koroshetz W, Krainc D, Lazic SE, Levine MS, Macleod MR, McCall JM, Moxley RT, 3rd, Narasimhan K, Noble LJ, Perrin S, Porter JD, Steward O, Unger E, Utz U, Silberberg SD (2012) A call for transparent reporting to optimize the predictive value of preclinical research Nature 490: 187-191
15. Li M, Caeyenberghs K (2018) Longitudinal assessment of chemotherapy-induced changes in brain and cognitive functioning: A systematic review Neuroscience and biobehavioral reviews 92: 304-317
16. Lv L, Mao S, Dong H, Hu P, Dong R (2020) Pathogenesis, Assessments, and Management of Chemotherapy-Related Cognitive Impairment (CRCI): An Updated Literature Review Journal of Oncology 2020: 3942439
17. Macleod MR, Van Der Worp HB, Sena ES, Howells DW, Dirnagl U, Donnan GA (2008) Evidence for the efficacy of NXY-059 in experimental focal cerebral ischaemia is confounded by study quality Stroke 39: 2824-2829
18. Matsos A, Johnston IN (2019) Chemotherapy-induced cognitive impairments: A systematic review of the animal literature Neurosci Biobehav Rev 102: 382-399

19. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement Annals of internal medicine 151: 264
20. Moher D, Simera I, Schulz KF, Hoey J, Altman DG (2008) Helping editors, peer reviewers and authors improve the clarity, completeness and transparency of reporting health research BMC medicine 6: 1-3
21. Munir F, Burrows J, Yarker J, Kalawsky K, Bains M (2010) Women's perceptions of chemotherapy-induced cognitive side affects on work ability: a focus group study J Clin Nurs 19: 1362-1370
22. Myers JS (2009) Chemotherapy-related cognitive impairment: neuroimaging, neuropsychological testing, and the neuropsychologist.(Report) Clinical Journal of Oncology Nursing 13: 413
23. Nekhlyudov L, Mollica MA, Jacobsen PB, Mayer DK, Shulman LN, Geiger AM (2019) Developing a Quality of Cancer Survivorship Care Framework: Implications for Clinical Care, Research, and Policy J Natl Cancer Inst 111: 1120-1130
24. Nguyen LD, Ehrlich BE (2020) Cellular mechanisms and treatments for chemobrain: insight from aging and neurodegenerative diseases EMBO Molecular Medicine 12: e12075
25. Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M, Garner P, Holgate ST, Howells DW, Karp NA, Lazic SE, Lidster K, MacCallum CJ, Macleod M, Pearl EJ, Petersen OH, Rawle F, Reynolds P, Rooney K, Sena ES, Silberberg SD, Steckler T, Würbel H (2020) The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research PLOS Biology 18: e3000410
26. Player L, Mackenzie L, Willis K, Loh SY (2014) Women's experiences of cognitive changes or 'chemobrain' following treatment for breast cancer: a role for occupational therapy? Aust Occup Ther J 61: 230-240
27. Pound P, Ritskes-Hoitinga M (2020) Can prospective systematic reviews of animal studies improve clinical translation? Journal of Translational Medicine 18: 1-6
28. Santos JC, Pyter LM (2018) Neuroimmunology of Behavioral Comorbidities Associated With Cancer and Cancer Treatments.(Report)(Author abstract) Frontiers in Immunology 9
29. Seigers R, Fardell JE (2011) Neurobiological basis of chemotherapy-induced cognitive impairment: A review of rodent research Neuroscience and biobehavioral reviews 35: 729-741
30. Seigers R, Loos M, Van Tellingen O, Boogerd W, Smit AB, Schagen SB (2016) Neurobiological changes by cytotoxic agents in mice Behavioural brain research 299: 19-26
31. Selamat MH, Loh SY, Mackenzie L, Vardy J (2014) Chemobrain experienced by breast cancer survivors: a meta-ethnography study investigating research and care implications PloS one 9: e108002-e108002
32. Simó M, Rifà-Ros X, Rodriguez-Fornells A, Bruna J (2013) Chemobrain: a systematic review of structural and functional neuroimaging studies Neuroscience and biobehavioral reviews 37: 1311-1321
33. Smith AJ, Clutton RE, Lilley E, Hansen KEA, Brattelid T (2018) PREPARE: guidelines for planning animal research and testing Laboratory Animals 52: 135-141
34. Taillibert S, Le Rhun E, Chamberlain MC (2016) Chemotherapy-Related Neurotoxicity Curr Neurol Neurosci Rep 16: 81
35. van der Worp HB, Macleod MR (2011) Preclinical studies of human disease: time to take methodological quality seriously Journal of molecular and cellular cardiology 51: 449-450
36. Vesterinen HM, Sena ES, Ffrench-Constant C, Williams A, Chandran S, Macleod MR (2010) Improving the translational hit of experimental treatments in multiple sclerosis Multiple Sclerosis Journal 16: 1044-1055
37. Vichaya EG, Chiu GS, Krukowski K, Lacourt TE, Kavelaars A, Dantzer R, Heijnen CJ, Walker AK (2015) Mechanisms of chemotherapy-induced behavioral toxicities Frontiers in Neuroscience 9
38. Walker AK, Chang A, Ziegler AI, Dhillon HM, Vardy JL, Sloan EK (2018) Low dose aspirin blocks breast cancer-induced cognitive impairment in mice PloS one 13: e0208593-e0208593

566 39. Wang XM, Walitt B, Saligan L, Tiwari AF, Cheung CW, Zhang ZJ (2015) Chemobrain: a
567 critical review and causal hypothesis of link between cytokines and epigenetic
568 reprogramming associated with chemotherapy Cytokine 72: 86-96
569 40. Wefel JS, Schagen SB (2012) Chemotherapy-Related Cognitive Dysfunction Current
570 neurology and neuroscience reports 12: 267-275
571 41. Winocur G, Johnston I, Castel H (2018) Chemotherapy and cognition: International cognition
572 and cancer task force recommendations for harmonising preclinical research Cancer Treat
573 Rev 69: 72-83

574
575