

Research Waste in ME/CFS

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Abstract

Objective: To compare the prevalence of selective reporting in ME/CFS research areas: psychosocial versus cellular.

Method: A bias appraisal was conducted on three trials (1x psychosocial and 2x cellular) to compare risk of bias in study design, selection and measurement. The primary outcome compared evidence and justifications in resolving biases by proportions (%) and ORs (Odds Ratio); the secondary outcome determined the proportion (in %) of ME/CFS grants at risk of bias.

Results: NS (cellular study) was twice as likely to present evidence in resolving biases over PACE (psychosocial trial) (OR = 2.16; 65.6% vs 46.9%), but this difference was not significant ($p = 0.13$). However, NS was five times more likely to justify biases over PACE (OR = 4.76; 46.9% vs 15.6%) and this difference was significant ($p = 0.0095$; $p < 0.05$). PACE was weak in place (operational aspects 32%) and NS for data practices (37%). The proportion of grants were more biased in PACE (72%) than NS (28%) for evidence, and also more biased in PACE (86%) than NS (14%) for justifications.

Conclusion: Psychosocial trials on ME/CFS are more likely to engage in selective reporting indicative of research waste than cellular trials. Improvements to place may help reduce these biases, whereas cellular trials may benefit from adopting more translatable data methods. However, these findings are based on two trials. Further risk of bias appraisals are needed to determine the number of trials required to make robust these findings.

Keywords: Research Waste, Selective Reporting, PACE, Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, Clinical Trials, Research Integrity, Evidence-Based Medicine, E-utilities

1. Background

Research waste in clinical trials are seen in outcomes that are not published, or in selective reporting of incidental and spurious findings that cannot be reproduced or translated in practice. When outcomes are not published: resources are wasted, research is stilted, and the study protocol cannot be validated nor repudiated in future protocols. Reviews on publication rates indicate: 50% of randomised trials are not published (Kasenda *et al.*, 2014); 88% for cohort studies (Bogert *et al.*, 2015); and 50% for pre-clinical and clinical studies (Schmucker *et al.*, 2014). On the other hand, selective reporting is suspected when data is fabricated (intentionally misrepresented); or falsified (intentionally manipulated) in favour of a desired outcome. The potential causes of selective reporting include: poor recruitment, irrelevant endpoints, biased selection criteria and discontinuation, for instance: of 1017 RCTs, 25% were discontinued, and of those, 9.9% were discontinued due to poor recruitment (Kasenda *et al.*, 2014). When outcomes are not published, authors are contacted for missing data in instances of imputing data in unpublished trials (systematic review). However in selective reporting, even if the reported outcomes appear distinctly remarkable: *p* hacking (extremely good *p* values); file drawer problem (only positive results), it is difficult to substantiate who is responsible for it, and whether it was intentional; and whether institutional enquiries into research misconduct are worth pursuing if proven to be futile against existing policies, and run the risk of polarising research communities.

As clinical trials become more complex, there is increasing concern selective reporting is harder to detect, and unforeseen complexities may escalate between the oversight bodies that monitor research integrity (eg. issues of research misconduct) versus the autonomy which allow research communities to freely conduct their own research. This review seeks to demonstrate these complexities in Chronic Fatigue Syndrome (CFS).

2. ME/CFS

Myalgic Encephalomyelitis (ME) and CFS are not yet considered distinct diagnoses, but have been in the past (White *et al.*, 2007). The time to onset and the causes of these fatigue-like symptoms are confined to case studies (low evidence), and is still debated among experts. Nevertheless, both are diagnosed when there is an absence of fatigue-related disorders, and

36 the patient achieves a minimum threshold score for ME/CFS in at least one
37 fatigue questionnaire eg. The Chalder Fatigue Scale; The Krupp Fatigue
38 Severity Scale; DePaul Symptom Questionnaire etc. (Board on the Health
39 Select Populations, 2015).

40 In the UK, Cognitive Behavioural Therapy (CBT) and Graded Exercise
41 Therapy (GET) are proposed treatment regimens for ME/CFS to reduce the
42 symptoms of fatigue (NICE guidelines), and are based on the results of a
43 randomised trial (PACE: Pacing, graded Activity, and Cognitive behaviour
44 therapy) on ME/CFS patients ($n = 641$) conducted between March 2005 and
45 November 2008. It recommends 12 to 15 sessions of Cognitive Behavioural
46 Therapy (CBT; Fatigue: $n = 161$, $p = 0.0136$, $p < 0.05$) over 52 weeks; or
47 12 to 14 sessions of Graded Exercise Therapy (GET; Fatigue: $n = 159$, p
48 $= 0.0013$, $p < 0.05$) over 52 weeks (White *et. al.*, 2011). ME/CFS support
49 groups have rejected this treatment regimen due to harms from post-exertion
50 malaise after GET, and no improvements after CBT. Biomolecular findings
51 further support these claims with evidence of cellular level harms detected af-
52 ter GET (Cook *et. al.*, 2017), and have proposed biomarkers that are unique
53 to ME/CFS (Fluge *et. al.*, 2016). The consensus is that ME/CFS is a com-
54 plex, multi-faceted disorder that requires a multi-disciplinary approach, and
55 aetiologies at multiple angles, such as: gut microbiota, hormonal, endocrine
56 and immune functions. However, psychosocial angles can also offer impor-
57 tant insights when studies are designed based on evidence. The following are
58 lessons learnt from PACE, and recommendations on evidence-based study
59 designs that may facilitate biomolecular studies, and potentially salvage psy-
60 chosocial perspectives from branching off into research waste.

61 **3. Methods**

62 *3.1. Search strategy*

63 Search terms “myalgic encephalomyelitis”, “cognitive”, “behaviour”, “gra-
64 ded exercised therapy”, “adaptive pacing therapy”, “gene”, “cell”, “clinical-
65 trials.gov” were automatically mined from PubMed using E-utilities on a
66 UNIX platform with no date restriction (fig. 1: sample code). The number
67 of articles, authors and grants were tabulated by year in Excel. All arti-
68 cles, authors, and grants were included, and none were excluded. The search
69 strategy collated MeSH terms for two research trends: Psychosocial versus
70 Cellular. Articles were not scoped (included or excluded) for quality to ob-
71 serve only for research trends, and to minimise selection bias in future studies

72 that may choose to replicate this search strategy. This search strategy did
73 not scope for treatment effects as done in systematic reviews, but on research
74 trends in selecting high impact trials for a bias appraisal.

```
esearch -db pubmed -query "myalgic  
encephalomyelitis  
AND clinicaltrials.gov[si]" | \  
efetch -format xml | \  
xtract -pattern Author -sep " " -element  
LastName,Initials
```

Figure 1: Sample search code in E-utilities (PubMed).

75 3.2. Bias appraisal

76 The author conducted a bias appraisal (an extended version of Cochrane’s
77 bias appraisal tool) on three articles based on search outcomes: year and
78 impact factor (fig. 2): 1. PACE: psychosocial interventions (GET, CBT,
79 and Adaptive Pacing Therapy) to represent psychosocial trends (White *et.*
80 *al.*, 2011); 2. A neural study (NS) on post-exertion malaise after GET to
81 represent cellular trends (Cook *et. al.*, 2017). 3. A gut study (GS) on
82 profiling gut microbial differences in ME/CFS individuals (Giloteaux *et. al.*,
83 2017) to also represent cellular trends. In table 1, biases were categorised
84 by: “study design”, “selection” and “measurement.” Each potential bias was
85 rated by the author with a plus (+) or a minus sign (-) to indicate whether
86 a study presented evidence (E) or a justification (J) for resolving a potential
87 bias. The first two columns E and J rated PACE (White *et. al.*, 2011). The
88 next two columns E and J rated GS (Giloteaux *et. al.*, 2017); followed by
89 ratings for NS (Cook *et. al.*, 2017). The column “Neural Study” offered an
90 example of each rating from Cook and colleagues’ (2017) paper. The column
91 “Potential Biases” defined these biases in public health terms. The far right
92 column with the letters “T”, “P”, “D”, “R”: Theory (theories and models
93 used in the trial); Place (operational conduct); Recruitment (participant
94 recruitment); Data (data practices) were collated to predict the areas of
95 strengths and weaknesses (selective reporting) in each trial.

96 3.3. Statistical analysis

97 1. Primary outcome

PACE TRIAL	STUDY DESIGN	PACE		GUT		NEURAL		NEURAL STUDY	POTENTIAL BIASES	AREAS
		E	J	E	J	J	E			
Answers clinical questions eg. PICO		-	-	+	+	+	+	Evidence & justification of harms.	Reporting bias	T
Type of treatment for each therapy arm		+	-	-	-	+	+	Evidence & justification for intervention.	Performance bias	T
Treatment administered parallel or cross-modal		+	-	-	-	-	-	No evidence & justification for mode type.	Performance bias	T
Endpoints (treatment time-frame)		-	-	-	-	-	+	Evidence of endpoints, no justification.	Detection bias	T
Pre-registered trial		+	+	-	-	-	-	Not pre-registered.	Reporting bias	T
Site-specific assessment		-	-	+	+	+	+	Evidence of place & justification for place.	Performance bias	P
Validated clinical trial protocol		-	-	+	-	+	+	Evidence & justification for protocol.	Detection bias	T
Validated standard operating procedures		-	-	+	-	+	+	Evidence of SOP, justification for imaging.	Performance bias	P
Pre-trial risk assessments		-	-	-	-	+	+	Extension of previous work.	Performance bias	T
Pre-trial research eg. systematic review		+	-	+	+	+	+	Literature on alleviating harms.	Reporting bias	T
Blinding of staff and participants		-	+	-	-	-	-	No blinding.	Performance bias	P
Blinding of outcome assessment		+	+	-	-	-	-	No blinding.	Detection bias	P
SELECTION										
Correct population sample		+	-	+	-	+	+	Evidence & justification for characteristics.	Misclassification (non-differential)	R
Random sequence generation		+	+	-	-	-	-	No randomisation.	Misclassification (differential)	D
Allocation concealment		-	+	-	-	-	-	No allocation concealment.	Misclassification (differential)	P
Inclusion criteria		+	-	-	-	+	+	Evidence & justification for inclusion.	Misclassification (differential)	R
Exclusion criteria		+	-	-	-	-	+	Evidence of exclusion but no justification.	Misclassification (non-differential)	R
Programmer's institution or software		-	-	-	-	+	+	Evidence of software & justification for use.	Misclassification (differential)	D
Baseline measures		+	-	+	-	+	+	Evidence & justification for baseline measures.	Misclassification (differential)	R
Validated patient questionnaires		-	-	-	-	+	+	Evidence & justification: inter-rater reliability.	Misclassification (non-differential)	P
MEASUREMENT										
Data collection procedure		-	-	+	+	-	-	Unspecified.	Systematic error	P
Data collection instruments		-	-	+	+	+	+	Evidence & justification for instruments.	Systematic error	P
Data storage		-	-	+	+	+	+	Evidence & justification for image storage.	Systematic error	P
Missing data		+	-	-	-	-	-	Unspecified.	Attrition bias	D
Sample sizes		+	-	-	-	-	+	Evidence of sample size but no justification.	Misclassification (non-differential)	R
Power calculations		+	-	-	-	-	-	Unspecified.	Misclassification (non-differential)	T
Statistical methods		+	-	+	-	-	+	Evidence of methods but no justification.	Misclassification (differential)	T
Validity		-	-	-	-	+	+	Control group for comparison.	Misclassification (non-differential)	T
Repeatability		-	-	-	-	-	-	No mention of similar results to other studies.	Misclassification (non-differential)	T
Minimise confounding		-	-	-	-	-	-	Multiple questionnaires/exposures problematic.	Misclassification (non-differential)	P
Frequency of exposure		+	-	-	-	-	+	No justification for repeated exposure.	Systematic error	P
Frequency of outcome		-	-	-	-	-	+	Evidence of outcomes, frequency not justified.	Random error	P
	Total +	20	17	36						

Figure 2: Summary of bias ratings. “+” sign indicates evidence or justifications present in the trial, “-” sign indicates it was not present. Areas “T”, “P”, “D”, “R” stand for Theory, Place, Data and Recruitment to represent the potential weak areas in the trial.

98 ME/CFS research trends: psychosocial or cellular were compared using
 99 a 2x2 contingency table to determine the strength of evidence (table 1)
 100 and justifications (table 2). Columns E and J from the bias appraisal
 101 (fig. 2) were tallied and imputed into two contingency tables, and its
 102 proportions were compared in deriving the Odds Ratio (OR). The OR
 103 determined the strength of evidence or justifications in resolving biases
 104 between the two research trends. It also determined the likelihood (in
 105 %) of evidence or justifications that were present in each research trend.
 106 Finally, Z tests (two-tailed) were performed to assess whether the use
 107 of evidence or justifications were significantly different between the two

108 research trends.

109 2. Secondary outcome

110 The OR (primary outcome) was applied to the total number of ME/CFS
111 grants (search strategy) declared in each research trend (psychosocial
112 versus cellular) to compare the proportion (in %) of grants at risk of
113 bias.

114 3. Software

115 All data were imputed and analysed by the author using a web-based
116 clinical trials calculator (Centre for Clinical Research and Biostatistics,
117 The Chinese University of Hong Kong) and verified for accuracy in
118 another web-based, effect-size calculator (Campbell Collaboration).

Evidence	E+	E-
NS	21	11
PACE	15	17

Table 1: 2x2 contingency table comparing evidence tallied from figure 2 (bias appraisal). NS stands for Neural Study; E+ for total plus ratings; E- for total minus ratings.

Justification	J+	J-
NS	15	17
PACE	5	27

Table 2: 2x2 contingency table comparing justification tallied from figure 2 (bias appraisal). NS stands for Neural Study; J+ for total plus ratings; J- for total minus ratings.

119 **4. Results**

120 The search strategy identified 1750 published articles for psychosocial
121 ME/CFS research and 1015 for cellular ME/CFS research between the dates
122 1951 to 25 March 2017 (day the search was performed). All articles were
123 included in observing research trends: psychosocial versus cellular (fig. 1).
124 Of interest were altmetric scores scoped manually in a psychosocial trial
125 from 2011 (PACE; White *et. al.*, 2011); a cellular study from 2016 (NS;
126 Cook *et. al.*, 2017); and another cellular study from 2016 (GS; Giloteaux
127 *et. al.*, 2016). All articles were selected for popularity (altmetric scores) to
128 represent ME/CFS research trends: 1. Psychosocial: PACE trial (White *et.*

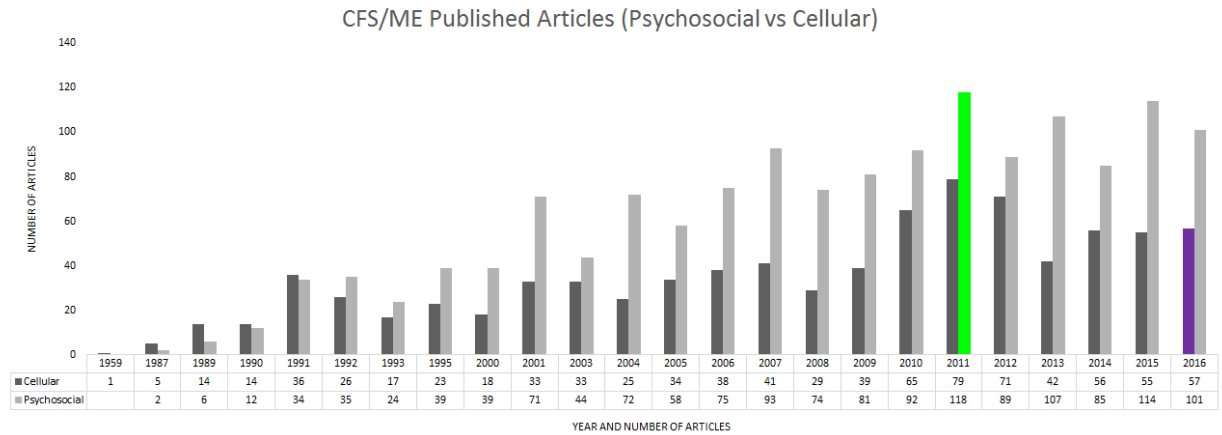


Figure 3: Search results comparing research trends: psychosocial versus cellular by year and number of published articles. The highlighted portions denote which year studies were selected for the bias appraisal.

129 *al.*, 2011); 2. Cellular: Neural study (Cook *et. al.*, 2017); 3. Cellular: Gut
 130 study (Giloteaux *et. al.*, 2016) however, did not undergo any further analysis,
 131 since pre-trial conditions (eg. serum samples) from the bias appraisal (table
 132 1) were significantly different in scope to the other two studies *ie.* it did not
 133 conform to an *intention to treat* experimental design.

134 4.1. Risk of bias appraisal

135 1. Study design

136 The study design for PACE was unclear, it was neither a randomised
 137 controlled trial (no control group) nor a cohort study (randomised);
 138 whereas NS had a control group and was likely a case-control study.
 139 All of which may have influenced performance biases, attrition biases
 140 and other operational biases towards or away from the null. PACE had
 141 four treatment arms all ending in 52 weeks but these endpoints were not
 142 justified. NS also did not justify measuring neural endpoints in 3 days.
 143 Hence both studies were potentially biased on whether treatment effects
 144 were measured at an optimal level for a true effect. PACE registered
 145 the trial (ISRCTN54285094), NS did not, however, it did specify the
 146 site in which the intervention took place, whereas PACE did not, which
 147 are potential causes of attrition and reporting biases particularly when
 148 trial results can not be verified. NS based the intervention off prior work

149 and used objective instruments (imaging scans) for measuring outcomes
150 of an appropriate sample size; PACE on the otherhand, recruited a
151 large sample size for an early phase trial, with no evidence of pre-trial
152 risk assessments on standard operating procedures and clinical trial
153 protocols which normally recruit small sample sizes in early phase trials
154 (so to limit risks on the population of interest). The study design for
155 GS was unclear, it did not conform to an intention to treat experimental
156 design. It had a control group which were matched to cases, but it did
157 not specify the number of specimens, patients and controls recruited
158 by the physician, and if diagnostic tests *ie.* blood draws were done
159 after an already confirmed ME/CFS diagnosis, which are all potential
160 causes of performance, attrition and other biases.

161 2. Selection bias

162 NS presented evidence and justifications for population sampling, base-
163 line measures between cases and controls (patient characteristics), and
164 validated questionnaires prior to conducting the study, but it did not
165 conceal treatment allocations despite including a control group. This
166 is highly problematic and can lead to selection biases consistent in
167 case studies without a control group (low evidence). Conversely, if NS
168 used a case-control design, it fell short of blinding and a good coverage
169 of cases obtained from all facilities (not just one) to minimise selec-
170 tion bias. PACE presented better clinical protocols but did not justify
171 population sampling, sample size, selection criteria, baseline measures,
172 questionnaires and software. GS presented very little evidence and jus-
173 tifications in selection eg. it did not specify the number of participants
174 and baseline measures that were relevant to sourcing serum samples.
175 All of which are potential causes of selection bias.

176 3. Measurement bias

177 All three studies were scant on evidence and justifications for data
178 collection, analysis and dissemination. PACE did not specify who col-
179 lected data, the types of software used, or whether the interventions
180 were curative (given there were no treatment endpoints) and relevant
181 to clinical practice. NS did not specify on which specialists assessed
182 the imaging scans and whether the imaging scans were sufficiently sen-
183 sitive and specific in diagnosing ME/CFS. Also, there was no blind-
184 ing (if case-control), neither did it specify the number of participants
185 screened per questionnaire (eg. information about lost controls) which
186 often leads to biases in underestimating the prevalence of exposure in

187 controls, and overestimate the Odds Ratio in favour of cases (those
188 with ME/CFS). GS presented evidence and justifications for assessing
189 data in a controlled lab environment, but it did not specify any missing
190 data or contaminated samples, any lab errors, confounding or overlap-
191 ping of RNA sequences with other disease conditions. It also used a
192 rank statistical method, an unspecified machine learning method, a
193 sub-sampling method for validating an unspecified model, all of which
194 were unclear and potential causes of measurement bias.

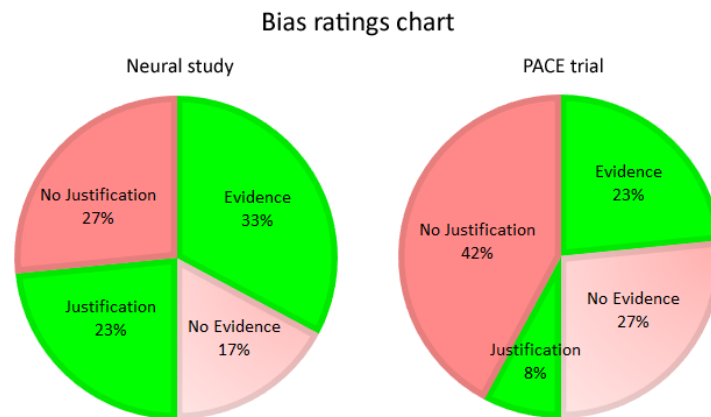


Figure 4: The proportion of bias in evidence and justifications in NS and PACE.

195 4.2. Evidence ratings

196 NS was twice as likely to be supported by evidence compared to PACE
197 (OR = 2.16). NS strength of evidence was at 65.6% and 33% relative to
198 justifications; for PACE 46.9% and 23% relative to justifications (fig. 4).
199 However, there was no significant difference between the two studies in pre-
200 senting evidence to resolve biases ($p = 0.13$; $p > 0.05$).

201 4.3. Justification ratings

202 NS was five times more likely to address biases compared to PACE (OR
203 = 4.76). Justifications present in NS were at 46.9% and 23% relative to evi-
204 dence; for PACE 15.6% and 8% relative to evidence (fig. 4). Unlike evidence,
205 there was a significant difference in presenting justifications to resolve biases
206 in favour of NS ($p = 0.0095$; $p < 0.05$).

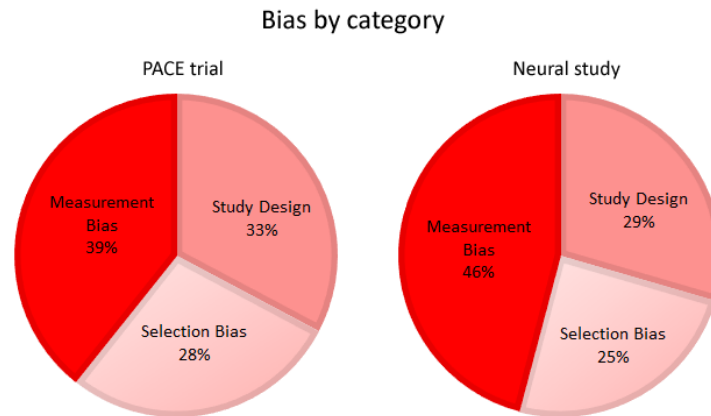


Figure 5: The proportion of bias by category in PACE and NS.

207 *4.4. Proportion of bias*

208 Measurement bias was the most prevalent of all biases: PACE (39%) and
209 NS (46%); followed by bias in study design: PACE (33%) and NS (29%);
210 followed by selection bias: PACE (28%) and NS (25%) (fig. 5).

211 *4.5. Study weaknesses*

212 PACE was weak in place (32%) and theory (28%), whereas NS was weak
213 in data (37%) and place (28%) (fig. 6).

214 *4.6. Grants at risk of bias*

215 The proportion of ME/CFS grants declared in psychosocial publications
216 were at 56% ($n = 722$; number of articles; search dates 1951 to 25 March
217 2017) and 44% ($n = 568$) for cellular. The proportion of grants biased in
218 presenting evidence for psychosocial were at 71.8% and 28.2% for cellular
219 (OR = 2.16; fig. 7). Grants biased in presenting justifications were at 86.4%
220 for psychosocial and 13.6% for cellular (OR = 4.76; fig. 7).

221 **5. Discussion**

222 The results suggest psychosocial ME/CFS trials are more likely to engage
223 in selective reporting than cellular ME/CFS trials. It confirms the concerns
224 raised by ME/CFS groups that psychosocial interventions are harmful, and
225 present questionable therapeutic benefits no different to a placebo (Childs *et.*

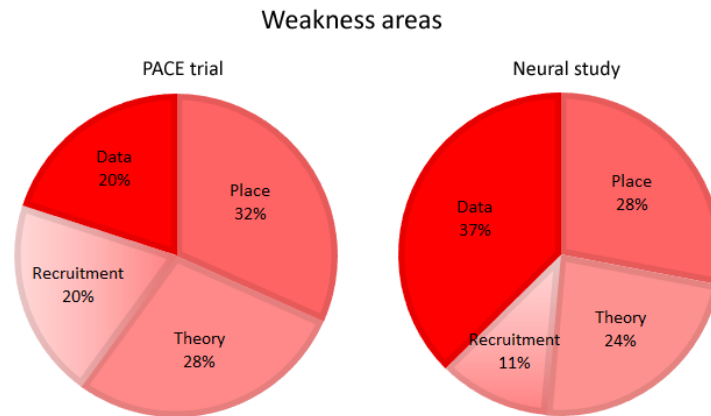


Figure 6: The proportion of weakness areas in PACE and NS.

226 *al.*, 2015; Lian & Nettleton, 2015). However, the results also suggest, cellular
227 trials are also likely to engage in selective reporting, but its therapeutic ben-
228 efit is difficult to assess, since no study as of yet have proposed a therapeutic
229 agent (eg. drug) exclusively designed and marketed for treating ME/CFS
230 (Collatz *et. al.*, 2016). Brurberg and colleagues (2014) propose the need for
231 consistency in ME/CFS research by applying a diagnostic criteria, subject
232 to a systematic evaluation. This need to adequately define ME/CFS is a
233 recurring consensus among researchers (Jason, Boulton & Friedberg, 2010;
234 Nacul *et. al.*, 2011; Johnston *et. al.*, 2013). Some propose a re-evaluation
235 of domains and criteria in existing patient reported outcome measurements
236 (PROMs) by considering subgroups to account for heterogeneity (different
237 populations) in comorbid conditions (eg. thyroid issues) and patient char-
238 acteristics (eg. children) (Nacul *et. al.*, 2011; Haywood, Staniszevska &
239 Chapman, 2012; Johnston *et. al.*, 2014; Haywood, Collin & Crawley, 2014;
240 Hvidberg *et. al.*, 2015; Murdock *et. al.*, 2016). Others propose the need
241 to investigate biomarkers and immune-mediated networks in developing a
242 prophylactic agent (Fuite, Vernon & Broderick, 2008; Schlauch *et. al.*, 2016;
243 Vega *et. al.*, 2017; Armstrong *et. al.*, 2017).

244 If in the latter, cellular trials (eg. biomarkers, immune checkpoints etc.)
245 may benefit from designing outcomes which are sensitive and specific for
246 clinical practice, also safe and reproducible across clinical practice. If this
247 is not feasible, then begin with pre-clinical models (eg. animal models) and
248 confirm risk thresholds (endpoints; safety) to deter heterogeneity (diverse

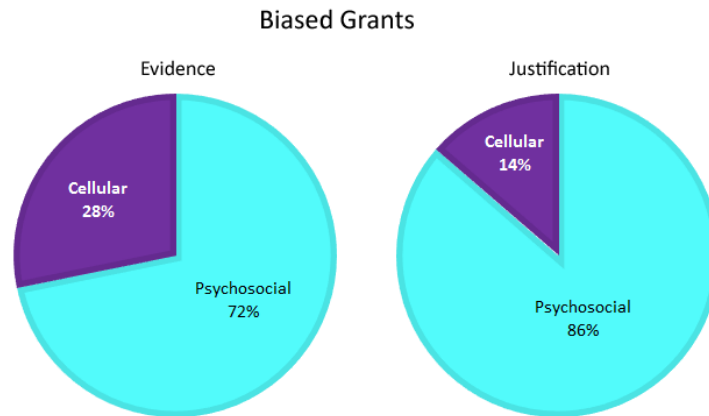


Figure 7: The proportion of bias in ME/CSF grants between research areas: psychosocial and cellular.

249 or novel methods) in clinical phases from biasing the true effect. On the
250 other hand, psychosocial studies (itemising and validating PROMs), may
251 benefit from ensuring operational aspects (place) are well documented and
252 archived. This ensures selective reporting in measurement- systematic errors
253 and misclassification effects (bias towards or away from the null) can be
254 corrected, and do not misconstrue the true effect.

255 Selective reporting is a problem in research waste, and a bias appraisal
256 on evidence and justifications is one way to bring light of this. Future studies
257 may look at biases (reoccurring problems) across multiple studies consistent
258 in each research area, so that oversight bodies (eg. grant committees) do not
259 restrict researchers from freely conducting research by enforcing a general
260 standard across all research areas to address research waste.

261 *Acknowledgements*

262 I dedicate this to ME Awareness Week 2017. I would like to thank ME
263 groups for your passionate advocacy and for sharing your stories with me.
264 It's truly inspiring. Thank you. A special shout out to @postersandme
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266 @consent_patient @chrisbrownofca1 @FrancieSaidSo @EllieArnott @JaneEBSmith
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268 helpful comments to this manuscript; and @DrFulli for attracting me to this
269 issue.

270 **Supplementary material**

271 Link to figures and codes:

272 http://www.openwetware.org/wiki/User:Sonia_Lee/Notebook/ResearchWasteMECFS

273 Link to slides:

274 https://figshare.com/articles/PACE_Trial_Critical_Appraisal_slides_/4685074

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